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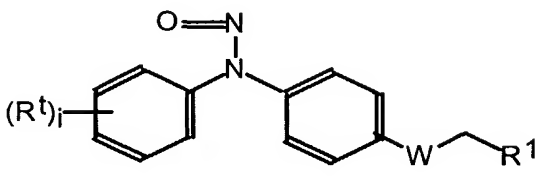
(54) Title: NITROSO DIPHENYLAMINE DERIVATIVES AS NITROGEN MONOXIDE GENERATING AGENTS



(I)

(57) Abstract: The present invention relates to compounds of the formula (I): in which: W, R^t, i and R^1 are as defined in Claim 1, that can be used for treating pathologies characterized by an oxidative stress condition and a lack of availability of endothelial nitrogen monoxide (NO°).

NITROSO DIPHENYLAMINE DERIVATIVES AS NITROGEN MONOXIDE GENERATING AGENTS

The invention relates to nitroso diphenylamine derivatives, to pharmaceutical compositions comprising them and to their use for preparing medicinal products that can be used for treating pathologies characterized by an oxidative stress condition and a lack of availability of endothelial nitrogen monoxide ($NO^{\bullet}$).

Nitrogen monoxide (or nitric oxide $NO^{\bullet}$) is an important mediator in the physiology of cardiovascular, immune and central and peripheral nervous systems. It acts, among other mechanisms, by activation of guanylate cyclase.

Its action is ubiquitous: it is vasodilatory and gives a basal tonus to the entire vascular system. It has anti-clotting activity: its production by normal endothelial cells inhibits the formation of a thrombus. It is anti-proliferative, especially on the smooth muscle cells underlying the endothelial cells. It also inhibits the adhesion of monocytes to the vascular wall and, consequently, its conversion to a macrophage. It regulates endothelial permeability.

There is thus, in the physiological state, a situation of equilibrium between the production of free-radical species and the availability of NO.

Disequilibrium of this balance, the result of which is an excess of superoxide anions in the face of a lack of NO, leads to the development of many pathologies.

Oxidative stress is generated by many factors, for instance hyperglycaemia, dyslipidaemias (production of oxidized, highly atherogenic "low-density" lipoproteins (LDL)), hypoxia, insulin resistance, atherosclerosis, revascularization techniques (including angioplasties with or without a stent), chronic rejection after transplantation, the majority of inflammatory processes, and addiction to smoking. Oxidative stress is characterized at the vascular level by an increase in free radicals, in particular of superoxide anions ($O_2^{\bullet -}$).

These $O_2^{\bullet-}$ radicals are capable of trapping the NO endogenously produced by the endothelial cells to form free-radical species that are even more deleterious, for instance peroxynitrites.

Among the pathologies concerned by a lack of production of endothelial nitrogen monoxide and/or an increase in tissue oxidative stress, mention may be made of (Recent Progress in Hormone Research (1988), 53, 43-60, table V):

- atherosclerosis-associated ischaemias (lipid peroxidation, development, progress and rupture of atheroma plaques, platelet activation);
- restenosis after angioplasty;
- stenosis after vascular surgery;
- diabetes;
- insulin resistance;
- retinal and renal microvascular complications of diabetes;
- the cardiovascular risk of diabetes in so far as it is not explained by the conventional factors;
- male erectile dysfunction;
- cerebral hypoxia;
- chronic rejection after organ transplantation;
- articular pathologies.

The administration of active principles capable of reducing the biological activity of oxidative free-radical species (such as superoxide anions and peroxynitrites) and of increasing the content of nitrogen monoxide by a two-fold mechanism: non-conversion into peroxynitrites and exogenous supply, is thus particularly desirable in the treatment of these pathologies.

The present invention provides compounds that have these two effects, antioxidant and nitrogen monoxide-donating, in the same molecule.

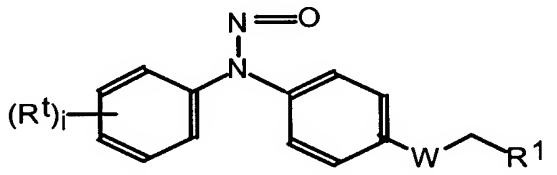
These compounds are capable of spontaneously generating nitrogen monoxide under physiological conditions and of trapping oxidative free radicals.

The spontaneous NO-donating effect does not induce a tachyphylactic effect, unlike compounds that are substrates of NO synthase, and unlike nitro

derivatives or derivatives of oxadiazole or oxatriazole type which mobilize endogenous thiols groups to release NO.

Via the spontaneous NO-donating effect, pharmacological NO activity may be achieved in pathologies in which the activity of NO synthase is insufficient.

More specifically, the invention relates to the compounds of the formula I:



I

in which:

- W represents O or S;

- the radicals R^t, which may be identical or different, represent a halogen atom; a saturated or unsaturated aliphatic hydrocarbon group, optionally interrupted by O and/or S and optionally halogenated; nitro; carboxyl or cyano;

- i represents an integer from 0 to 5, preferably 0, 1 or 2;

- R^1 represents an optionally substituted saturated, unsaturated and/or aromatic heterocyclic radical; an optionally substituted saturated, unsaturated and/or aromatic carbocyclic radical; -E-Q, in which E represents optionally substituted alkylene or alkenylene and Q represents an amino group which is optionally substituted by one or two saturated or unsaturated aliphatic hydrocarbon groups; or -E-Ar, in which E is as defined above and Ar represents an optionally substituted saturated, unsaturated and/or aromatic carbocyclic radical or alternatively an optionally substituted saturated, unsaturated and/or aromatic heterocyclic radical; or an optionally halogenated, saturated aliphatic hydrocarbon group;

with the exclusion of the compounds of the formula I in which i is 1; R^t represents 2-methyl and R^1 represents $-CH_3$, and their pharmaceutically tolerable derivatives, solvates and stereoisomers.

Hydrates and solvates are understood as meaning, for example, the hemi-,

mono- or dihydrates, solvates are understood as meaning, for example, alcohol addition compounds such as, for example, with methanol or ethanol.

The term pharmaceutically tolerable derivatives is taken to mean, for example, the salts of the compounds according to the invention and also so-called prodrug compounds.

The term prodrug derivatives is taken to mean, for example, compounds of the formula I which have been modified with, for example, alkyl or acyl groups, sugars or oligopeptides and which are rapidly cleaved in the organism to give the effective compounds according to the invention.

These also include biodegradable polymer derivatives of the compounds according to the invention, as described, for example, in Int. J. Pharm. 115, 61-67 (1995).

The invention also relates to mixtures of the compounds of the formula I according to the invention, for example mixtures of two diastereomers, for example in the ratio 1:1, 1:2, 1:3, 1:4, 1:5, 1:10, 1:100 or 1:1000.

These are particularly preferably mixtures of stereoisomeric compounds.

The expression "halogen atom" means a fluorine, chlorine, bromine or iodine atom, preferably a chlorine or fluorine atom.

The expression "aliphatic hydrocarbon group" means a hydrocarbon group containing a linear or branched chain, preferably containing from 1 to 14 carbon atoms, preferably from 1 to 10 and better still from 1 to 6 carbon atoms, for example from 1 to 4 carbon atoms.

Examples of saturated aliphatic hydrocarbon groups are alkyl radicals such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, isopentyl, neopentyl, 2-methylbutyl, 1-ethylpropyl, hexyl, isohexyl, neohexyl, 1-methylpentyl, 3-methylpentyl, 1,1-dimethylbutyl, 1,3-dimethylbutyl, 2-ethylbutyl, 1-methyl-1-ethylpropyl, heptyl, 1-methylhexyl, 1-propylbutyl, 4,4-dimethylpentyl, octyl, 1-methylheptyl, 2-methylhexyl, 5,5-dimethylhexyl, nonyl, decyl, 1-methylnonyl, 3,7-dimethyloctyl and 7,7-dimethyloctyl.

If the aliphatic hydrocarbon group is unsaturated, it may contain one or two unsaturations. The unsaturations are either of the ethylenic or acetylenic type. They are preferably ethylenic. The unsaturated chains contain at least two carbon atoms.

Alkenyl and alkynyl groups are examples of unsaturated aliphatic hydrocarbon groups.

Examples of unsaturated aliphatic hydrocarbon groups are allyl and vinyl.

The expression "optionally interrupted by O and/or S" means that any carbon atom of the hydrocarbon chain may be replaced with an oxygen or sulfur atom, where it is not possible for this carbon atom to be located at the free end of the hydrocarbon chain. The hydrocarbon chain, which may be alkyl, may contain a plurality of oxygen and/or sulfur atoms, the hetero atoms preferably being separated from each other by at least one carbon atom and better still by at least two carbon atoms.

An example of an aliphatic hydrocarbon chain which is interrupted by O or S is alkoxy or thioalkoxy.

In the context of the invention, the expression "saturated, unsaturated and/or aromatic cyclic (carbocyclic or heterocyclic) radical" means that the same radical may contain a saturated moiety and/or an unsaturated moiety and/or an aromatic moiety.

The carbocyclic and heterocyclic radicals include mono- and polycyclic radicals; these radicals preferably denote mono-, bi- or tricyclic radicals. In the case of polycyclic radicals, it should be understood that these consist of monocycles fused in pairs (for example ortho-fused or peri-fused), i.e. having at least two carbon atoms in common. Preferably, each monocycle is 3- to 8-membered and better still 5- to 7-membered.

The heterocyclic groups comprise hetero atoms generally chosen from O, N and S, optionally in oxidized form (in the case of S and N).

Preferably, each of the monocycles constituting the heterocycle contains from 1 to 4 hetero atoms and better still from 1 to 3 hetero atoms.

Examples of aromatic heterocyclic groups are 5- to 7-membered monocyclic heteroaryls, such as pyridine, furan, thiophene, pyrrole, pyrazole, imidazole, thiazole, isoxazole, isothiazole, furazane, pyridazine, pyrimidine, pyrazine, thiazines, oxazole, pyrazole, oxadiazole, triazole and thiadiazole.

Examples of unsaturated 7-membered heterocycles include trithiatriazepines and trithiadiazepines. Examples of 5- to 7-membered saturated monocyclic heterocycles especially include tetrahydrofuran, dioxolane, imidazolidine, pyrazolidine, piperidine, dioxane, morpholine, dithiane, thiomorpholine, piperazine, trithiane, oxepine and azepine.

Examples of aromatic bicyclic heterocyclic groups in which each monocycle is 5- to 7-membered are indolizine, indole, isoindole, benzofuran, benzopyran, benzothiophene, indazole, benzimidazole, benzothiazole, benzofurazane, benzothiofurazane, purine, quinoline, isoquinoline, cinnoline, phthalazine, quinazoline, quinoxaline, naphthyridines, pyrazolotriazine (such as pyrazolo-1,3,4-triazine), pyrazolopyrimidine and pteridine groups.

The saturated and unsaturated derivatives of these groups are examples of saturated, or unsaturated, bicyclic heterocyclic groups.

Examples of aromatic tricyclic heterocyclic groups are those consisting of 5- to 7-membered monocycles such as acridine or carbazole.

The aromatic carbocyclic radicals are preferably C_6-C_{18}. Among these, mention may be made especially of phenyl, naphthyl, anthryl and phenanthryl radicals.

Saturated carbocyclic radicals are especially cycloalkyl radicals, preferably C_3-C_{18} and better still C_3-C_{10} cycloalkyl radicals, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, adamantyl or norbornyl.

The unsaturated carbocyclic groups comprise one or more, preferably 1 to 3, ethylenic double bonds and generally consist of 6 to 18 and better still from 6 to 10 carbon atoms. Examples of these are cycloalkenyl radicals, and especially cyclohexenyl radicals.

According to the invention, "alkylene" represents a linear or branched divalent hydrocarbon chain containing from 1 to 14, preferably from 1 to 10 and

better still from 1 to 6 carbon atoms, for example from 1 to 4 carbon atoms. Preferred examples of alkylene chains are methylene, ethylene and propylene chains. The term "alkenylene" means a linear or branched, divalent aliphatic hydrocarbon chain comprising one or more ethylenic unsaturations. Examples of these are C_2-C_{14} and preferably C_2-C_{10} chains, for example C_2-C_6 chains, such as -CH=C- and -CH=CH-CH_2-.

In a particularly advantageous manner, R^1 represents an optionally substituted aromatic carbocyclic radical; an optionally substituted aromatic heterocyclic radical; an optionally substituted heterocyclic radical with an aromatic moiety; -E-Q, in which E represents alkylene and Q represents amino, alkylamino or dialkylamino; -E-Ar, in which E represents alkenylene and Ar represents an optionally substituted aromatic carbocyclic radical, an optionally substituted aromatic heterocyclic radical or an optionally substituted radical with an aromatic moiety.

According to the invention, the expression "heterocycle with an aromatic moiety" means a heterocycle consisting of one or more monocycles each preferably being 5- to 7-membered, in which at least one of the monocycles is aromatic and at least one of the monocycles is heterocyclic, and in which the monocycles are ortho- or peri-fused in pairs. It should be understood that the non-aromatic monocycles may be saturated or unsaturated and that the aromatic monocycle is heterocyclic or non-heterocyclic. Furthermore, at least one of the monocycles of the heterocycle with an aromatic moiety is non-aromatic. The heterocyclic monocycle(s) contain(s) one or more endocyclic hetero atoms (preferably 1 to 4 and better still 1 to 3) chosen from O, N and S, optionally in oxidized form (in the case of S or N).

The carbocyclic aromatic monocycles of the heterocycle with an aromatic moiety are preferably phenyl nuclei.

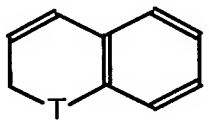
The heterocyclic aromatic monocycles of the heterocycle with an aryl moiety are preferably pyridine, furan, thiophene, pyrrole, pyrazole, imidazole, thiazole, isoxazole, isothiazole, furazane, pyridazine, pyrimidine, pyrazine, thiazine, oxazole, oxadiazole, triazole or thiadiazole nuclei.

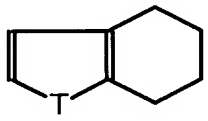
The heterocyclic saturated monocycles of the heterocycle with an aryl moiety are, for example, tetrahydrofuran, dioxolane, imidazolidine, pyrazolidine, piperidine, dioxane, morpholine, dithiane, thiomorpholine, piperazine, trithiane, oxepine or azepine nuclei. The heterocycle with an aryl moiety may contain one or more unsaturated monocycles derived from the aromatic or heterocyclic monocycles described above.

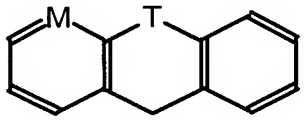
The heterocycle with an aryl moiety is mono- or polycyclic, preferably bi- or tricyclic.

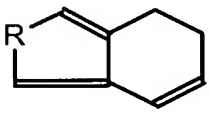
It should be understood that each of the saturated and/or unsaturated monocycles of the heterocycle with an aryl moiety may be substituted by oxo.

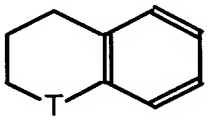
Examples of heterocycles with an aryl moiety are especially the nuclei of the formulae:

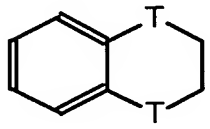
B1 : 

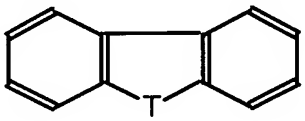
B2 : 

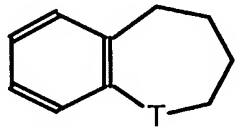
B3 : 

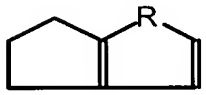
B4 : 

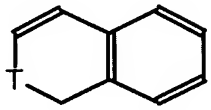
B5 : 

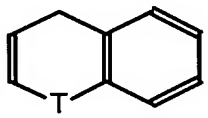
B6 : 

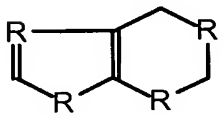
B7 : 

B8 : 

B9 : 

B10 : 

B11 : 

B12 : 

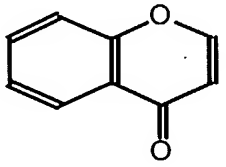
in which M and T are chosen, independently, from O, S, SO_2, N and C, it being understood that each of the nuclei B1 to B12 comprises at least one hetero atom optionally in oxidized form, and R is chosen from O, S and N.

According to the preferred embodiments of the invention:

T represents O, S or SO_2 and M represents N or C. Preferably, in B1, T represents O ; in B2, T represents O or S ; in B3, T represents SO_2 or O and M represents C or N ; in B4, R represents S ; in B5, T represents O ; in B6, T represents O ; in B7, T represents O ; in B8, T represents O ; in B9, R represents S ; in B10, T represents O ; in B11, T represents O ; in B12, R represents N.

If M, T or R represents N, it is preferably substituted by a hydrogen atom, alkyl or alkylcarbonyl.

Preferably, the heterocycle with an aryl moiety has the formula:



A preferred sub-group of the compounds of the invention consists of compounds for which R^1 represents optionally substituted phenyl; optionally substituted naphthyl; optionally substituted pyridyl; optionally substituted quinolyl; optionally substituted benzofuryl; optionally substituted oxazolyl; aminoalkyl; alkylaminoalkyl; dialkylaminoalkyl; optionally substituted coumarinyl; phenylalkenylene in which the phenyl nucleus is optionally substituted; 4-oxo-4H-benzopyranyl.

The substituents on the carbocyclic and heterocyclic groups are preferably chosen from oxo; optionally halogenated alkyl; optionally halogenated alkoxy; cyano; halogen; carboxyl; alkylcarbonyl; alkoxycarbonyl; and aryl itself optionally substituted by alkyl, alkoxy, halogen, cyano or nitro. The oxo radical is a substituent of the saturated or unsaturated nuclei.

More generally, the substituent is chosen from halogen atoms and the following groups: cyano; carboxyl; nitro; optionally halogenated (C_1-C_{14})alkoxy (and preferably trifluoromethoxy); optionally halogenated (C_1-C_{14})thioalkoxy, preferably (C_1-C_{10})thioalkoxy; optionally halogenated and preferably perhalo (C_1-C_{14})alkyl (and especially methyl or trifluoromethyl); (C_1-C_{14})alkylcarbonyl in which the alkyl moiety is optionally halogenated; (C_1-C_{14})alkoxycarbonyl in

which the alkoxy moiety is optionally halogenated; (C_6-C_{18})arylcarbonyl in which the aryl moiety is optionally substituted one or more times by halogen, optionally halogenated (C_1-C_{14})alkyl and optionally halogenated (C_1-C_{14})alkoxy; (C_1-C_{14})-alkylcarbonylamino in which the alkyl moiety is optionally halogenated; (C_6-C_{18})-arylcarbonylamino, in which the aryl is optionally substituted one or more times by halogen, optionally halogenated (C_1-C_{14})alkyl and optionally halogenated (C_1-C_{14})alkoxy; and (C_6-C_{18})aryl which is optionally substituted one or more times by halogen, optionally halogenated (C_1-C_{14})alkyl, such as trifluoromethyl, and optionally halogenated (C_1-C_4)alkoxy, such as trifluoromethoxy.

The heterocyclic and carbocyclic groups may be substituted one or more times by one or more of the substituents listed above, preferably one to three times, for example once or twice.

Preferably, R^t represents:

C_1-C_4 alkoxy; optionally halogenated C_1-C_4 alkyl; halogen; cyano; C_1-C_4 alkylthio; or carboxyl.

The invention is directed not only towards the compounds of the formula I, but also towards the salts thereof.

If the compound of the formula I contains an acid function, and for example a carboxylic function, this compound may form a salt with a mineral or organic base.

Examples of salts with organic or mineral bases that may be mentioned include the salts formed with metals and especially alkali metals, alkaline-earth metals and transition metals (such as sodium, potassium, calcium, magnesium or aluminium) or with bases, for instance ammonia or secondary or tertiary amines (such as diethylamine, triethylamine, piperidine, piperazine or morpholine) or with basic amino acids, or with osamines (such as meglumine) or with amino alcohols (such as 3-aminobutanol and 2-aminoethanol).

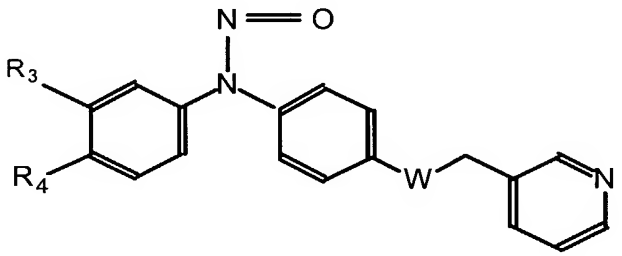
If the compound of the formula I contains a basic function, and for example a nitrogen atom, this compound may form a salt with an organic or mineral acid.

The salts with organic or mineral acids are, for example, the hydrochloride, hydrobromide, sulfate, hydrogen sulfate, dihydrogen phosphate, nitrate, trifluoroacetate, citrate, maleate, fumarate, 2-naphthalenesulfonate and para-toluenesulfonate.

The invention also covers salts that allow a suitable separation or crystallization of the compounds of the formula I, such as picric acid, oxalic acid or an optically active acid, for example tartaric acid, dibenzoyltartaric acid, mandelic acid or camphorsulfonic acid. However, a preferred sub-group of salts consists of salts of the compounds of the formula I with pharmaceutically acceptable acids or bases.

Formula I includes all the types of geometrical isomers and stereoisomers of the compounds of the formula I.

The compounds illustrated in the examples are preferred. Among these compounds, mention will be made more specifically of the following compounds of the formula:



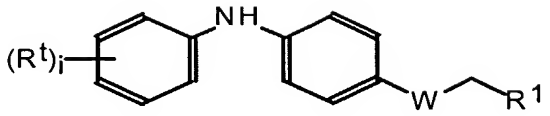
Ia

in which:

- W = O ; (R_3 , R_4) = (-H, 4-cyano) : Example 29b
- W = O ; (R_3 , R_4) = (-H, 3-cyano) : Example 31b
- W = S ; (R_3 , R_4) = (-H, 4-methoxy) : Example 26b
- W = O ; (R_3 , R_4) = (-H , 4-chloro) : Example 28b

it being understood that (R_3 , R_4) = (a , b) means that one from among R_3 and R_4 represents a and the other represents b.

The compounds of the invention may be simply prepared by nitrosation of the corresponding compounds of the formula II, of the formula:



II

in which R^t, i, W and R^1 are as defined above for formula I, by the action of a suitable nitrosating agent.

Particularly advantageous examples of nitrosating agents are an alkali metal nitrite (and especially sodium or potassium nitrite) or a C_1-C_4 alkyl nitrite.

A preferred alkali metal nitrite that may be mentioned is sodium nitrite.

A preferred alkyl nitrite that may be mentioned is ethyl nitrite.

Nevertheless, a person skilled in the art can use any nitrosating agent known in the art, such as AgONO, BF_4NO, $HOSO_3NO$, nBuONO and tBuONO.

The amount of nitrosating agent required depends on the nature of the nitrosating agent used and on the reactivity of the substrate of the formula II. It is at least stoichiometric. In general, the molar ratio of the nitrosating agent to the substrate of the formula II ranges between 1 and 30 equivalents and preferably between 1 and 20 equivalents.

If the nitrosating agent is an alkali metal nitrite, a person skilled in the art may readily adapt the reaction conditions so as to use only 1 to 10, preferably from 1 to 5 and better still from 1 to 3 equivalents of nitrite relative to the substrate of the formula II.

If the nitrosating agent is an alkyl nitrite, it is preferable to perform the process in the presence of 10 to 25 molar equivalents of nitrite, and preferably from 15 to 20 molar equivalents, relative to the amount of substrate of the formula II.

The choice of solvent and the temperature conditions depend especially on the type of nitrosating agent selected for the reaction.

If the nitrosating agent is AgONO, nBuONO or tBuONO, the solvent is advantageously chosen from a cyclic or non-cyclic ether (such as diethyl ether, diisopropyl ether, tetrahydrofuran, dioxane, dimethoxyethane or diethylene glycol dimethyl ether), an aliphatic or aromatic halohydrocarbon (such as chloro-

form, carbon tetrachloride, dichloroethane, chlorobenzene or dichlorobenzene). Preferably, the solvent is tetrahydrofuran, diethyl ether or chloroform.

The reaction temperature will generally be maintained between 15 and 70°C and better still between 17 and 60°C, in the case of AgONO, nBuONO and tBuONO.

More particularly, in the case of AgONO and nBuONO, the process will be performed in tetrahydrofuran or diethyl ether at a temperature of between 15 and 30°C, for example between 18 and 25°C.

In the case of tBuONO, the process will preferably be performed in chloroform at a temperature of between 40 and 65°C, for example between 50 and 60°C.

If the nitrosating agent is AgONO, it is desirable to add thionyl chloride to the reaction medium.

If the nitrosating agent is $HOSO_3NO$, the reaction is preferably carried out in an alkali metal salt of a lower (C_1-C_5) carboxylic acid, such as sodium acetate, at a reaction temperature of between -10°C and 30°C and better still between -5°C and 25°C.

If the nitrosating agent is BF_4NO, a suitable solvent is a nitrile such as acetonitrile or isobutyronitrile. It is desirable to add pyridine or N-dimethylaminopyridine to the reaction medium, the reaction temperature being maintained between -30°C and 10°C and preferably between -25°C and 5°C.

If the nitrosating agent is an alkali metal nitrite, the nitrosation reaction is preferably carried out in a strongly polar protic medium. The reaction medium advantageously comprises water and a Brönsted or Lewis acid.

Suitable acids are a hydrohalic acid (such as HCl), sulfuric acid, $Al_2(SO_4)_3$ and acetic acid, and mixtures thereof.

According to one particular embodiment of the invention, an aliphatic alcohol of (C_1-C_4)alkanol type (such as methanol or butanol) may be added.

Thus, a suitable reaction medium that may be selected is one of the following systems:

- a mixture of methanol, water, hydrochloric acid and sulfuric acid;
- a mixture of water and sulfuric acid;

- a mixture of water and acetic acid;
- a mixture of water, butanol and hydrochloric acid;
- a mixture of water and $Al_2(SO_4)_3$, or
- a mixture of water and hydrochloric acid.

The reaction of the alkali metal nitrite with the substrate of the formula II is advantageously carried out in a mixture of acetic acid and water, the ratio of the acetic acid to water ranging between 80:20 and 20:80 and preferably between 60:40 and 40:60, for example a 50:50 mixture. According to one preferred embodiment, the alkali metal nitrite, predissolved in water, is added dropwise to a solution of the substrate of the formula II in acetic acid.

The reaction of the alkali metal nitrite with the substrate of the formula II is carried out at a temperature which depends on the reactivity of the species present; this temperature generally ranges between -10°C and 50°C and preferably between -5°C and 25°C.

When the nitrosation reaction is carried out in a mixture of acetic acid and water, a temperature of between 15°C and 25°C is particularly suitable.

The reaction of the alkyl nitrite with the substrate of the formula II is preferably carried out in the presence of a C_1-C_4 alkanol in a polar aprotic solvent.

Suitable alkanols that may be mentioned include methanol, ethanol, isopropanol and tert-butanol, ethanol being particularly preferred.

Preferred polar solvents are halohydrocarbons, such as methylene chloride, chloroform, carbon tetrachloride, dichloroethane, chlorobenzene or dichlorobenzene; ethers such as diethyl ether, diisopropyl ether, tetrahydrofuran, dioxane, dimethoxyethane or diethylene glycol dimethyl ether; nitriles such as acetonitrile or isobutyronitrile; amides such as formamide, dimethylformamide, dimethylacetamide, N-methyl-2-pyrrolidinone or hexamethylphosphoramide; and mixtures of these solvents in any proportions.

The nitrosation reaction (if an alkyl nitrite is used as nitrosating agent) is advantageously carried out in a mixture based on an aliphatic halohydrocarbon

and a nitrile, and for example in a 90:10 to 50:50 and preferably a 90:10 to 70:30 mixture of chloroform and acetonitrile, in the presence of ethanol.

The amount of alkanol that needs to be incorporated into the reaction medium is not critical according to the invention. It generally represents 5% to 50% by weight of the reaction medium, and preferably from 5% to 25% by weight.

If the nitrosating agent is an alkyl nitrite, the reaction temperature is generally maintained at between -20°C and 20°C and preferably at between -10°C and 10°C, for example at between 0°C and 5°C.

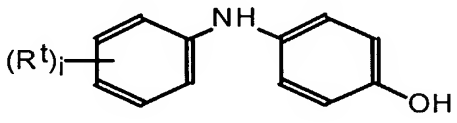
According to one preferred embodiment of the invention, a solution of the alkyl nitrite in the alkanol is added dropwise to the substrate of the formula II predissolved in the selected polar solvent.

As a variant, the reaction is carried out in a strongly polar medium consisting of a mixture of a C_1-C_4 aliphatic carboxylic acid ((C_1-C_4)alkyl-COOH), the corresponding acid anhydride and the corresponding alkali metal carboxylate salt, in the presence of P_2O_5. By way of example, a reaction medium consisting of acetic acid, acetic anhydride, potassium acetate and P_2O_5 may be selected. In this case, the reaction temperature is advantageously maintained between 10°C and 100°C and preferably between 15°C and 85°C.

The compounds of the formula II may be prepared by carrying out one of the following processes.

A - Preparation of the compounds of the formula II in which W represents O

One method for preparing the compounds of the formula II in which W represents O consists in reacting a compound of the formula III:



III

in which:

R^t and i are as defined above for formula II, with a compound of the formula IV :

$$T\text{-}CH_2\text{-}R^1 \qquad IV$$

in which T represents a leaving group and R^1 is as defined above for formula II.

Examples of suitable leaving groups are halogen atoms (and especially a chlorine or bromine atom) and groups of the formula $-O\text{-}SO_2$-alk and $-O\text{-}SO_2$-Ar in which alk represents an optionally halogenated alkyl group such as trifluoromethyl or methyl and Ar represents phenyl which is optionally substituted by alkyl, which is itself optionally halogenated.

This reaction is preferably carried out in the presence of an organic or mineral base. Examples of bases are hydroxides (such as alkali metal hydroxides or ammonium hydroxides), carbonates (such as alkali metal carbonates or ammonium carbonates), alkali metal alkoxides, organic hydrides, alkali metal amides, ammonia and amines of the type such as triethylamine, tributylamine, pyridine or N-methylmorpholine.

The reaction of the alcohol III with the compound of the formula IV is advantageously carried out in the presence of caesium carbonate as base.

According to one preferred embodiment of the invention, if T does not represent an iodine atom, it is desirable to add to the reaction medium a few crystals of alkali metal iodide, in catalytic amount.

This reaction is preferably performed in a polar aprotic solvent such as a halohydrocarbon (for example methylene chloride, chloroform, carbon tetrachloride, dichloroethane, chlorobenzene or dichlorobenzene); an ether such as diethyl ether, diisopropyl ether, tetrahydrofuran, dioxane, dimethoxyethane or diethylene glycol dimethyl ether; a nitrile such as an acetonitrile or isobutyronitrile; an amide such as formamide, dimethylformamide, dimethylacetamide, N-methyl-2-pyrrolidinone or hexylmethylphosphorylamide; or a ketone such as acetone or 2-butanone. The solvent is preferably acetone or 2-butanone.

The reaction temperature is set as a function of the reactivity of the species present and the nature of the solvent used. The temperature generally ranges

between -10°C and 100°C. Usually, when the base used is an alkali metal or alkaline-earth metal carbonate, the process is performed at the reflux temperature of the solvent. In a particularly advantageous manner, the reaction of the alcohol III with the compound IV is carried out in the presence of Cs_2CO_3, in a ketone solvent (such as acetone or 2-butanone) at a temperature of between 40 and 70°C.

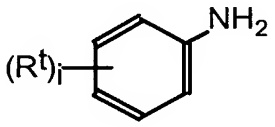
Usually, the molar ratio of compound IV to compound III ranges between 0.8 and 2, preferably between 1 and 1.5, for example between 1.1 and 1.3, a slight excess of compound IV being desirable.

The amount of base to be introduced into the reaction medium is generally an excess relative to the molar amount of the compound of the formula III. Preferably, the molar ratio of the base used to the compound III ranges between 1 and 2 equivalents, for example between 1.1 and 1.3 equivalents.

To carry out this reaction, a person skilled in the art may be inspired by Synthetic Comm. (1995), 25, 1367 - 1370.

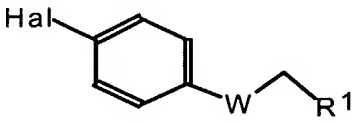
B - General method for preparing the compounds of the formula II

As a variant, the compounds of the formula II may be prepared by reacting an amine of the formula V:



V

in which R^t and i are as defined above for formula II, with a compound of the formula VI:



VI

in which W and R^1 are as defined above for formula II and Hal represents a halogen atom such as bromine or chlorine, preferably bromine. This reaction is advantageously carried out in the presence of a base. Examples of bases that may be selected are any one of those mentioned above. Preferably, an alkali metal alkoxide such as sodium or potassium methoxide, ethoxide or tert-butoxide will

be selected, and will be introduced into the reaction medium in a proportion of 1 to 2 equivalents per one equivalent of compound VI, for example between 1.2 and 1.7 equivalents.

This reaction is generally carried out at a temperature of between 50 and 180°C and preferably at a temperature of between 80 and 150°C. The temperature depends on the nature of the species present and especially the strength of the base and the reactivity of the compounds V and VI present.

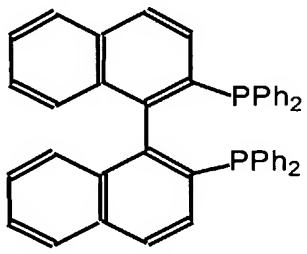
The solvent is generally chosen from the polar aprotic solvents defined above.

Preferred solvents that may be mentioned include ethers and especially glymes such as 1,2-dimethoxyethane, diethylene glycol dimethyl ether (diglyme) or triethylene glycol dimethyl ether (triglyme), diglyme being more particularly preferred.

According to one preferred embodiment of the invention, the molar ratio of the amine V to the compound VI ranges between 1 and 2 and better still between 1 and 1.5, for example between 1.1 and 1.3.

Advantageously, it is desirable to introduce a palladium(0) catalyst into the reaction medium.

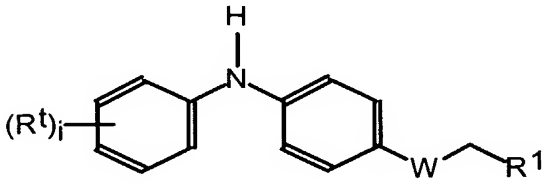
Such a catalyst may be obtained by introducing into the reaction medium the system $(dba)_3Pd_2$ (tris(dibenzylideneacetone)dipalladium(0)) + BINAP in which BINAP is the diphosphine of the formula:



By way of illustration, each of the catalytic substances $(dba)_3Pd_2$ and BINAP is introduced into the reaction medium in a proportion of less than 10% by weight. In a particularly advantageous manner, the molar ratio of the BINAP to the $(dba)_3Pd_2$ ranges between 1.5 and 4 and preferably between 2 and 3.

To carry out this reaction, a person skilled in the art may be inspired by J. Org. Chem. (2000), 65, 1144 - 1157.

The compounds of the formula II:



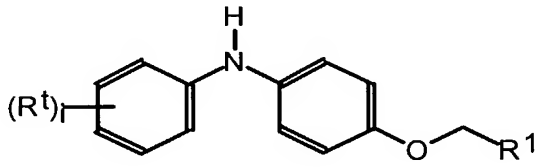
II

in which R^t and i are as defined for formula I, which are novel, form an integral part of the invention.

A first sub-group of these compounds consists of compounds in which W represents S.

More particularly, preferred compounds are those for which R^1 represents optionally substituted pyridyl, for example optionally substituted 3-pyridyl.

A second sub-group of these compounds is composed of the compounds of the formula IIa:



IIa

in which i and R^t are as defined above for formula I and R^1 represents optionally substituted naphthyl; unsubstituted pyridyl; optionally substituted coumarinyl; optionally substituted oxazolyl; optionally substituted benzoxazolyl; optionally substituted benzofuryl; optionally substituted 4-oxo-4H-benzo-pyranyl; cinnamyl which is optionally substituted on the phenyl nucleus; aminoalkyl; alkylaminoalkyl; or dialkylaminoalkyl; phenyl which is substituted by one or more substituents chosen from the following groups: cyano; carboxyl; nitro; halogenated (C_1-C_4)alkoxy (and preferably trifluoromethoxy); optionally halogenated (C_1-C_{14})thioalkoxy, preferably (C_1-C_{10})thioalkoxy; halogenated and preferably perhalo (C_1-C_{14})alkyl (and especially trifluoromethyl); (C_1-C_{14})alkylcarbonyl in which the alkyl moiety is optionally halogenated;

(C_1-C_{14})alkoxycarbonyl in which the alkoxy moiety is optionally halogenated; (C_6-C_{18})arylcarbonyl in which the aryl moiety is optionally substituted one or more times by halogen, optionally halogenated (C_1-C_{14})alkyl and optionally halogenated (C_1-C_{14})alkoxy; (C_1-C_{14})alkylcarbonylamino in which the alkyl moiety is optionally halogenated; (C_6-C_{18})arylcarbonylamino in which the aryl is optionally substituted one or more times by halogen, optionally halogenated (C_1-C_{14})alkyl and optionally halogenated (C_1-C_{14})alkoxy; and (C_6-C_{18})aryl optionally substituted one or more times by halogen, optionally halogenated (C_1-C_{14})alkyl, such as trifluoromethyl, and optionally halogenated (C_1-C_4)alkoxy, such as trifluoromethoxy;

with the exclusion of the compounds of the formula IIa in which R^1 represents dimethylaminomethyl; dimethylaminoethyl; and diethylaminomethyl.

It should moreover be noted that when R^1 represents dialkylaminoalkyl, it is preferred for R^1 to be dialkylamino(C_3-C_{10})alkyl or di(C_3-C_{10})alkylamino-(C_1-C_2)alkyl.

In addition, when R^1 represents substituted phenyl, the preferred substituents are cyano, halogenated (C_1-C_{14})alkyl, carboxyl and (C_1-C_{14})alkoxycarbonyl groups in which the alkoxy moiety is optionally halogenated, better still trifluoromethyl, cyano, carboxyl or methoxycarbonyl.

Among these compounds, preferred compounds are those for which R^1 represents optionally substituted pyridyl, for example optionally substituted 3-pyridyl.

In addition, for each of the sub-groups of compounds of the formula II defined above, preferred meanings of R^1 and R^t are those mentioned above.

Not only can the compounds of the formula II above be used as intermediates in the synthesis of the compounds of the formula I, but also they show antioxidant activity that makes them capable of limiting the destructive activity of oxidative free-radical species.

According to another of its aspects, the invention relates to a pharmaceutical composition comprising at least one compound of the formula I as

defined above, in combination with at least one pharmaceutically acceptable excipient.

According to yet another of its aspects, the invention relates to a pharmaceutical composition comprising at least one compound of the formula II, in combination with at least one pharmaceutically acceptable excipient.

These compounds may be administered orally in the form of tablets, gel capsules or granules with immediate release or controlled release, intravenously in the form of an injectable solution, transdermally in the form of an adhesive transdermal device, or locally in the form of a solution, cream or gel.

A solid composition for oral administration is prepared by adding to the active principle a filler and, where appropriate, a binder, a crumbling agent, a lubricant, a colorant or a flavour corrector, and by shaping the mixture into a tablet, a coated tablet, a granule, a powder or a capsule.

Examples of fillers include lactose, corn starch, sucrose, glucose, sorbitol, crystalline cellulose and silicon dioxide, and examples of binders include poly(vinyl alcohol), poly(vinyl ether), ethylcellulose, methylcellulose, acacia, gum tragacanth, gelatin, shellac, hydroxypropylcellulose, hydroxypropylmethylcellulose, calcium citrate, dextrin and pectin. Examples of lubricants include magnesium stearate, talc, polyethylene glycol, silica and hardened plant oils. The colorant may be any colorant permitted for use in medicinal products. Examples of flavour correctors include cocoa powder, mint in herb form, aromatic powder, mint in oil form, borneol and cinnamon powder. Needless to say, the tablet or granulate may be suitably coated with sugar, gelatin or the like.

An injectable form containing the compound of the present invention as active principle is prepared, where appropriate, by mixing the said compound with a pH regulator, a buffer agent, a suspending agent, solubilizing agent, a stabilizer, a tonicity agent and/or a preserving agent, and by converting the mixture into a form for intravenous, subcutaneous or intramuscular injection, according to a conventional process. Where appropriate, the injectable form obtained may be freeze-dried by a conventional process.

Examples of suspending agents include methylcellulose, polysorbate 80, hydroxyethylcellulose, acacia, powdered gum tragacanth, sodium carboxymethylcellulose and polyethoxylated sorbitan monolaurate.

Examples of solubilizing agents include castor oil solidified with polyoxyethylene, polysorbate 80, nicotinamide, polyethoxylated sorbitan monolaurate and the ethyl ester of castor oil fatty acid.

In addition, the stabilizer encompasses sodium sulfite, sodium metasulfite and ether, while the preserving agent encompasses methyl p-hydroxybenzoate, ethyl p-hydroxybenzoate, sorbic acid, phenol, cresol and chlorocresol.

The substances according to the invention are as a rule preferably administered in doses between approximately 0.1 and 100 mg, in particular between 1 and 10 mg, per dose unit. The daily dose is preferably between approximately 0.001 and 10 mg/kg of body weight. The specific dose for each patient, however, depends on all sorts of factors, for example on the efficacy of the specific compound employed, on the age, body weight, general state of health, sex, on the diet, on the time and route of administration, on the excretion rate, pharmaceutical combination and severity of the particular disorder to which the therapy applies. Oral administration is preferred.

According to another of its aspects, the invention relates to the use of a compound of the formula I as defined above, for the preparation of a medicinal product for treating pathologies characterized by a lack of nitrogen monoxide production and/or an oxidative stress condition.

According to one of its final aspects, the invention relates to the use of a compound of the formula II for the preparation of an antioxidant medicinal product that may be used as a free-radical scavenger.

The nitrogen monoxide-donating effect of the compounds of the invention of the formula I may be demonstrated simply by carrying out the following procedure.

A solution of a compound of the invention spontaneously releases nitric oxide. The nitrite ions resulting therefrom are titrated by colorimetry by means of a specific reagent (Griess). To take account of any release of nitrate ions in addition to the nitrites, bacterial nitrate reductase is added to the reaction medium to reduce the nitrate ions formed.

The reactions and measurements are performed in transparent 96-well plates. The test products are dissolved at the time of use, at a concentration of 3 mM in dimethyl sulfoxide. 95 µl of a reagent containing nitrate reductase (0.18 U/ml in 100 mM pH 7.5 PBS buffer, 210 µM β-NADPH, 5 µM FAD) and 5 µl of the solution of the test product (final concentration of 150 µM) are then added to each well. After stirring, the mixtures are incubated for 4 hours at 37°C. The reaction is then stopped by adding 100 µl of Griess' reagent (Sigma G4410). The resulting mixture is stirred for 5 min at room temperature, and the optical density is then read at 540 nm. This value is proportional to the concentration of nitrites + nitrates in the medium. A calibration range is made for each plate, using $NaNO_2$.

The results obtained in the case of some of the compounds illustrated in the examples clearly show their ability to increase the level of nitric oxide. These results are collated in Table 1 below and expressed in µmol/l (µM) of nitrate + nitrite products:

TABLE 1

Example	Nitrites + nitrates (μM)
1b	92
2b	72
4b	28
20b	27
25b	43
26b	80
27b	68
28b	72
29b	85
30b	46
31b	84
32b	72
33b	81
35c	89

The compounds of the formula I and the compounds of the formula II of the invention show antioxidant activity, which makes them suitable for reducing the biological activity of oxidative free-radical species.

The antioxidant activity of the compounds of the formulae I and II is especially revealed *in vitro*, for example by evaluating their ability to prevent the chemical oxidation of low molecular weight human lipoproteins, as described previously (Table 2).

Human LDLs placed in aqueous solution in the presence of cupric ions, become spontaneously oxidized on their protein component, apolipoprotein-B. This oxidation makes the particle fluorescent, which is exploited to measure a pharmacological effect.

The reactions and measurements are performed in black 96-well plates. 10 µl of a solution of the test product dissolved in dimethyl sulfoxide are first mixed with 170 µl of a solution of human LDL at a concentration of 120 µg/ml and 20 µl of 100 µM $CuCl_2$. After stirring, the mixture is incubated for 2 hours at 37°C, and a first fluorescence reading is taken (excitation at 360 nm, reading at 460 nm). The mixture is then incubated for a further 22 hours, to take a second reading under the same conditions. The difference between the two values obtained is the measurement of the oxidation of the LDLs in solution. This difference is proportionately smaller the greater the antioxidant power of the test product. Probucol is used as reference product at a concentration of 10 µM.

The 50% inhibitory concentrations (IC_{50}) for the oxidation, obtained for some of the compounds of the invention, are given in Table 2 below. They are produced from three concentrations of product.

TABLE 2

Example	IC_{50} antioxidant effect (µM)
1a	4.6
1b	6.7
2b	5.1
4a	2.4
4b	9.3
7a	3.4
8a	4.0
15a	4.2
16a	3.3
18a	3.2
19a	4.5
20a	3.8
20b	7.0

23a	2.3
25a	2.0
25b	7.5
26a	7.2
27a	3.3
28a	7.3
33a	7.3
33b	11.3
34a	3.2

The present invention is illustrated below in the light of the following examples.

The frequency of the NMR machine used to record the proton spectra of the examples given below is 300 MHz.

s denotes a singlet; d denotes a doublet; t denotes a triplet; q denotes a quartet and m denotes a multiplet.

m.p. denotes the melting point.

The preparation of some of the compounds of the formulae I and II is more particularly detailed in the case of Examples 1, 2, 34 and 35 of the invention.

EXAMPLE 1

3-({4-[1-(4-methoxyphenyl)-2-oxohydrazino]phenoxy}methyl)pyridine

a) N-(4-methoxyphenyl)-N-[4-(pyrid-3-ylmethoxy)phenyl]amine (compound of the formula II : R^1 = 3-pyridyl ; W = O ; R^t = 4-OCH_3 ; i = 1)

0.54 g (3.28 mmol) of 3-chloromethylpyridine hydrochloride is added to a mixture of 0.53 g (2.74 mmol) of 4-[(4-methoxyphenyl)amino]phenol, prepared according to Chem. Abstr. (1958) 7183, and 1.8 g (5.48 mmol) of caesium carbonate in 15 ml of acetone. After stirring for 6.5 hours at reflux, the reaction medium is poured into water and extracted with ethyl ether. The organic phase is washed with water and then dried over Na_2SO_4 and concentrated under vacuum.

The residue, purified by chromatography on a column of silica in a heptane/ethyl acetate mixture (1/2), gives 0.54 g of a pink solid.

Yield : 64.2%.

m.p. = 100°C

NMR (DMSO-d6) δ (ppm) : 3.7 (3H, s) ; 5.1 (2H, s) ; 6.8 (2H, m) ; 6.9 (6H, m) ; 7.4 (1H, m) ; 7.6 (1H, s) ; 7.8 (1H, m) ; 8.5 (1H, m) ; 8.6 (1H, m).

b) 3-({4-[1-(4-methoxyphenyl)-2-oxohydrazino]phenoxy}methyl)pyridine (Compound of the formula I : R^1 = 3-pyridyl ; W = O ; R^t = 4-OCH_3 ; i = 1)

62 mg (0.898 mmol) of sodium nitrite in 2.4 ml of water are added to a solution under nitrogen of 250 mg (0.816 mmol) of N-(4-methoxyphenyl)-N-[4-(pyrid-3-ylmethoxy)phenyl]amine in 12.3 ml of acetic acid. The reaction medium is stirred for 3 hours at room temperature and then poured into 100 ml of water and extracted with ether.

The organic phase is washed with $NaHCO_3$ solution and then with water to pH 7, and dried over Na_2SO_4. After concentration and drying under vacuum, 261.7 mg of a red oil are obtained (Yield: 95.6%), which crystallizes slowly.

m.p. = 75-80°C

NMR (DMSO-d6) δ (ppm) : 3.8 (3H, 2s) ; 5.2 (2H, s) ; 7.0-7.5 (9H, m) ; 7.9 (1H, m) ; 8.6 (1H, m) ; 8.7 (1H, m).

EXAMPLE 2

3-{[4-(2-oxo-1-phenylhydrazino)phenoxy]methyl}pyridine

a) 3-[(4-bromophenoxy)methyl]pyridine

A mixture of 4.3 g (25 mmol) of 4-bromophenol, 16.3 g (50 mmol) of caesium carbonate, 0.1 g of KI, 4.95 g (30 mmol) of 3-chloromethylpyridine hydrochloride and 60 ml of acetone is refluxed for 8 hours and then poured into water and extracted with ether. The organic phase is washed with H_2O and dried over Na_2SO_4, and then concentrated to give an oil. Purification by chromatography on a column of silica in a heptane/ethyl acetate mixture (4/1) gives 5.9 g of a beige-coloured solid (yield: 89.4%).

NMR (DMSO-d6) δ (ppm) : 5.15 (2H, s) ; 7.0 (2H, m) ; 7.45 (3H, m) : 7.9 (1H, m) ; 8.5 (1H, m) ; 8.7 (1H, m).

b) N-phenyl-4-(pyrid-3-ylmethoxy)aniline

(compound of the formula II : R^1 = 3-pyridyl ; W = O ; i = 0).

26 mg (0.028 mmol) of tris(dibenzylideneacetone)dipalladium (0), 53 mg (0.085 mmol) of racemic BINAP (2,2-bis(diphenylphosphino)-1,1-binaphthyl) and 164 mg (1.71 mmol) of sodium tert-butoxide are added to a mixture under nitrogen of 0.3 g (1.14 mmol) of 3-[(4-bromophenoxy)methyl]pyridine and 0.127 g (1.39 mmol) of aniline in 8.7 ml of diglyme (diethylene glycol dimethyl ether).

The reaction medium is heated at 130°C for 18 hours, and then poured into 20 ml of water and extracted with ethyl acetate (20 ml). The organic phase, washed with water, is dried over Na_2SO_4 and then concentrated under vacuum. The residue obtained is purified by chromatography on a column of silica in a heptane/ethyl acetate mixture (1/1) to give 0.169 g of a solid (yield: 53.9%).

NMR (DMSO-d6) δ (ppm) : 5.1 (2H, s) ; 6.7 (1H, m) ; 6.9-7.2 (8H, m) ; 7.4 (1H, m) ; 7.9 (2H, m) ; 8.5 (1H, m) ; 8.7 (1H, m).

c) 3-{[4-(2-oxo-1-phenylhydrazino)phenoxy]methyl}pyridine

(compound of the formula I : R^1 = 3-pyridyl ; W = O ; i = 0) obtained by working as in Example 1b).

Yield : 98.3 %.

NMR (DMSO-d6) δ (ppm) : 5.2 (2H, 2s) ; 7.1-7.25 (4H, m) ; 7.3-7.6 (6H, m) ; 7.9 (1H, m) ; 8.6 (1H, m) ; 8.7 (1H, m).

EXAMPLE 34 :

4-({4-[1-(4-methoxyphenyl)-2-oxohydrazino]phenoxy}methylbenzoic acid

a) 4-({4-methoxyphenyl)amino]phenoxy}methyl)benzoic acid

(Compound of the formula II : R^1 = 4-carboxyphenyl ; W = O ; i = 1 ; R^t = 4-OCH_3)

62 mg (1.1 mmol) of KOH dissolved in 10 ml of water are added to a solution of 0.2 g (0.550 mmol) of methyl 4-({4-[(4-methoxyphenyl)amino]-phenoxy}benzoate prepared in Example 7a in 10 ml of ethanol.

After refluxing for 3 hours, the ethanol is concentrated and the residue is taken up in 100 ml of water and then washed with 2 × 100 ml of ether. The aqueous phase is then acidified with acetic acid. The precipitate formed is filtered off, washed with water and dried under vacuum to give 0.161 g of a grey solid (yield: 83%).

m.p. = 198-200°C

NMR (DMSO-d6) δ (ppm) : 3.9 (3H, s) ; 5.1 (2H, s) ; 6.8 (2H, d, J = 8.9 Hz) ; 6.9 (4H, s) ; 6.93 (2H, d, J=8.9 Hz) ; 7.5 (3H, m) ; 7.9 (2H, d, J = 8.2 Hz) ; 12.8 (1H, broad s).

b) 4-({4-[1-(4-methoxyphenyl)-2-oxohydrazino] phenoxy}methyl)benzoic acid

(compound of the formula I : R^1 = 4 – carboxyphenyl ; W = O ; i = 1 ; R^t = 4-OCH_3)

Obtained as in Example 1b.

NMR (DMSO-d6) (δ ppm) : 3.8 (3H, s) ; 5.25 (2H, s) ; 7.0-7.4 (8H, m) ; 7.6 (2H, m) ; 7.95 (2H, m) ; 13.0 (1H, broad s).

EXAMPLE 35

4-{2-oxo-1-[4-(pyrid-3-ylmethoxy)phenyl]hydrazino}benzoic acid

a) ethyl 4-{[4-(pyrid-3-ylmethoxy)phenyl]amino}benzoate

Obtained as in Example 2a starting with 3-[(4-bromophenoxy)methyl]-pyridine and ethyl 4-aminobenzoate.

NMR (DMSO-d6) (δ ppm) : 1.2 (3H, t, J = 7, 1Hz) ; 4.2 (2H, q, J = 7.1 Hz) ; 5.1 (2H, s) ; 6.9 (2H, m) ; 7.05 (2H, m) ; 7.15 (2H, m) ; 7.5 (1H, m) ; 7.75 (2H, m) ; 7.9 (1H, m) ; 8.5 (1H, s) ; 8.7 (1H, s) ; 12.1 (1H, broad s).

b) 4-{[4-(pyrid-3-ylmethoxy)phenyl]amino}benzoic acid

(Compound of the formula II : R^1 = 3-pyridyl ; W = O ; i = 1 ; R^t = 4-carboxy).

Obtained as in Example 34a starting with the ester prepared in Example 35a (53.8% yield).

m.p. = 222-224°C

NMR (DMSO-d6) (δ ppm) : 5.1 (2H, s) ; 6.9 (2H, d, J = 8.8 Hz) ; 7.0 (2H, m) ; 7.1 (2H, m) ; 7.4 (1H, m) ; 7.7 (2H, d, J = 8.7 Hz) ; 7.9 (1H, m) ; 8.5 (1H, s) ; 8.6 (1H, m) ; 8.7 (1H, m) ; 12.4 (1H, broad s).

c) 4-{2-oxo-1-[4-(pyrid-3-ylmethoxy)phenyl]hydrazino}benzoic acid

(Compound of the formula I : R^1 = 3-pyridyl ; W = O ; i = 1 ; R^t = 4-carboxy)

Obtained as in Example 2b (26.4% yield)

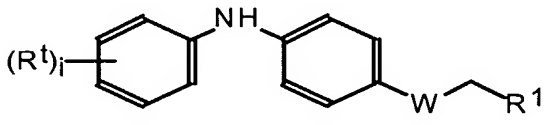
NMR (DMSO-d6) (δ ppm) : 5.2 (2H, s) ; 7.2 (4H, m) ; 7.35 (1H, m) ; 7.5 (3H, m) ; 7.9 (1H, m) ; 8.05 (2H, m) ; 8.6 (1H, m) ; 8.7 (1H, m)

The compounds of Examples 3 to 25 were obtained as in Example 1.

The compounds of Examples 27 to 33 were obtained as in Example 2.

The compounds of Example 26 were obtained as in Example 2, starting with 3-{[(4-bromophenyl)thio]methyl}pyridine, prepared according to Haviv F. et al., J. Med. Chem. (1983) 26, 218-222.

The compounds in Table 3 correspond to the following formula:

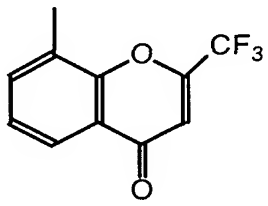


II

TABLE 3

Example No.	Reference	W	R^1	i	R^t	NMR δ (ppm)
3a	LR 20997	O	4-methoxyphenyl	1	4-OCH_3	($CDCl_3$) ; 3.78 (7H, 2s) ; 4.94 (2H, s) ; 6.75-7.05 (10H, m) ; 7.34 (2H, d, J = 8.54 Hz)
4a	LR 20998	O	3-trifluoromethyl-phenyl	1	4-OCH_3	($CDCl_3$) = 3.77 (3H, s) ; 5.06 (2H, s) ; 6.75-7.10 (8H, m) ; 7.40-7.80 (5H, m)
5a	LR21023	O	phenyl	1	4-OCH_3	(DMSO-d6) = 3.68 (3H, s) ; 5.01 (2H, s) ; 6.71-6.85 (2H, m) ; 6.85-7.00 (6H, m) ; 7.30-7.50 (5H, m) ; 7.53 (1H, s)
6a	LR 21024	O	—CH=CH(Ph)	1	4-OCH_3	(DMSO-d6) = 3.68 (3H, s) ; 4.64 (2H, dd, J=1.2 Hz, J=5.76 Hz) ; 6.40-6.60 (1H, m) ; 6.70-7.00 (9H, m) ; 7.20-7.40 (3H, m) ; 7.40-7.60 (3H, m)
7a	LR 21061	O	4-methoxycarbon-ylphenyl	1	4-OCH_3	(DMSO-d6) = 3.68 (3H, s) ; 3.85 (3H, s) ; 5.12 (2H, m) ; 6.75-7.00 (8H, m) ; 7.50-7.65 (3H, m) ; 7.90-8.05 (2H, m)
8a	LR 20999	O	1-naphthyl	1	4-OCH_3	(DMSO-d6) = 3.68 (3H, m) ; 5.46 (2H, m) ; 6.75-7.0 (8H, m) ; 7.45-7.70 (5H, m) ; 7.87-8.15 (3H, m)
9a	LR 21025	O	2-methylphenyl	1	4-OCH_3	(DMSO-d6) = 2.32 (3H, s) ; 3.69 (3H, s) ; 4.99 (2H, s) ; 6.75-7.05 (8H, m) ; 7.10-7.30 (3H, m) ; 7.35-7.50 (1H, m) ; 7.50-7.60 (1H, m)
10a	LR 21026	O	2-fluorophenyl	1	4-OCH_3	(DMSO-d6) = 3.69 (3H, s) ; 5.05 (2H, s) ; 6.77-7.00 (8H, m) ; 7.15-7.30 (2H, m) ; 7.35-7.48 (1H, m) ; 7.48-7.61 (2H, m)

11a	LR 21027	O	4-fluorophenyl	1	4-OCH_3	(DMSO-d6) = 3.68 (3H, s) ; 4.99 (2H, s) ; 6.80-7.00 (8H, m) ; 7.10-7.30 (2H, m) ; 7.40-7.65 (3H, m)
12a	LR 21028	O	4-ethylphenyl	1	4-OCH_3	(DMSO-d6) = 1.18 (3H, m) ; 2.60 (2H, m) ; 3.68 (3H, s) ; 4.97 (2H, s) ; 6.70-7.00 (8H, m) ; 7.15-7.40 (4H, m) ; 7.48-7.60 (1H, s)
13a	LR 21029	O	2-chlorophenyl	1	4-OCH_3	(DMSO-d6) = 3.69 (3H, s) ; 5.07 (2H, s) ; 6.71-7.04 (8H, m) ; 7.30-7.65 (5H, m)
14a	LR 21030	O	4-chlorophenyl	1	4-OCH_3	(DMSO-d6) = 3.68 (3H, s) ; 5.02 (2H, s) ; 6.75-7.00 (8H, m) ; 7.40-7.60 (5H, m)
15a	LR 21058	O	4-trifluoromethyl-phenyl	1	4-OCH_3	(DMSO-d6) = 3.68 (3H, s) ; 5.14 (2H, s) ; 6.75-7.00 (8H, m) ; 7.50-7.85 (5H, m)
16a	LR 21059	O	4-cyanophenyl	1	4-OCH_3	(DMSO-d6) = 3.68 (3H, s) ; 5.13 (2H, s) ; 6.75-7.05 (8H, m) ; 7.50-7.70 (3H, m) ; 7.70-7.95 (2H, m)
17a	LR 20785	O	2-cyanophenyl	0	-	(DMSO-d6) = 5.16 (2H, s) ; 6.65-6.85 (1H, m) ; 6.85-7.10 (6H, m) ; 7.10-7.65 (4H, m) ; 7.65-8.00 (3H, m)
18a	LR 21060	O	2,4-dichlorophenyl	1	4-OCH_3	(DMSO-d6) = 3.69 (3H, s) ; 5.06 (2H, s) ; 6.75-6.85 (2H, m) ; 6.85-7.00 (6H, m) ; 7.45-7.55 (1H, m) ; 7.55-7.65 (2H, m) ; 7.55-7.60 (1H, m)
19a	LR 21145	O	7-methoxycoumarin-4-yl	1	4-OCH_3	(DMSO-d6) = 3.68 (3H, s) ; 3.87 (3H, s) ; 5.30 (2H, s) ; 6.30-6.55 (1H, s) ; 6.73-7.18 (10H, m) ; 7.50-7.70 (1H, s) ; 7.70-7.85 (1H, m)
20a	LR 21146	O	2-phenyl-5-methyl-oxazol-4-yl	1	4-OCH_3	(DMSO-d6) = 2.43 (3H, s) ; 3.68 (3H, s) ; 4.91 (2H, s) ; 6.77-7.00 (8H, m) ; 7.45-7.65 (4H, m) ; 7.85-8.05 (2H, m)

21a	LR 21150	O	2-ethoxycarbonyl-5-benzofuryl	1	4-OCH_3	(DMSO-d6) = 1.34 (3H, t, J=7.06 Hz) ; 3.68 (3H, s) ; 4.36 (2H, q, J=7.06 Hz) ; 5.17 (2H, s) ; 7.75-7.90 (2H, m) ; 7.90-7.05 (6H, m) ; 7.40-7.68 (2H, m) ; 7.68-7.85 (2H, m) ; 7.85-7.95 (1H, m)
22a	LR 21151	O		1	4-OCH_3	(DMSO-d6) = 3.69 (3H, s) ; 5.28 (2H, s) ; 6.80-6.90 (2H, m) ; 6.90-7.00 (6H, m) ; 7.05-7.15 (1H, m) ; 7.50-7.70 (2H, m) ; 7.95-8.15 (2H, m)
23a	LR 21163	O	2-methoxy-5-acetyl-phenyl	1	4-OCH_3	(DMSO-d6) = 2.52 (3H, s) ; 3.57 (3H, s) ; 3.91 (3H, s) ; 5.01 (2H, s) ; 6.85-7.00 (8H, m) ; 7.10-7.25 (1H, m) ; 7.55 (1H, s) ; 7.90-8.10 (2H, m)
24a	LR 21178	O	quinol-2-yl	1	4-OCH_3	(DMSO-d6) = 3.67 (3H, s) ; 5.28 (2H, s) ; 6.75-7.05 (8H, m) ; 7.50-7.75 (3H, m) ; 7.75-7.85 (1H, m) ; 7.95-8.10 (2H, m) ; 8.35-8.50 (1H, m)
25a	LR 21107	O	diisopropylamino-methyl	1	4-OCH_3	(DMSO-d6) = 0.97 (12H, d, J=6.56 Hz) ; 2.72 (2H, t, J=7.08 Hz) ; 3.00 (2H, septet, J=6.56 Hz) ; 3.68 (3H, s) ; 3.79 (2H, t, J=7.08 Hz) ; 6.75-6.85 (4H, m) ; 6.85-6.95 (4H, m) ; 7.50 (1H, s, exchangeable)
26a	LR 21255	S	3-pyridyl	1	4-OCH_3	(DMSO-d6) = 3.71 (3H, s) ; 4.02 (2H, s) ; 6.85-7.20 (8H, m) ; 7.20-7.40 (1H, m) ; 7.55-7.70 (1H, m) ; 7.95-8.10 (1H, m) ; 8.30-8.50 (2H, m)
27a	388721	O	3-pyridyl	1	4-methyl	(DMSO-d6) = 2.19 (3H, s) ; 5.08 (2H, s) ; 6.85-7.10 (8H, m) ; 7.35-7.50 (1H, m) ; 7.65-7.90 (2H, m) ; 8.50-8.70 (2H, m)

28a	388723	O	3-pyridyl	1	4-chloro	(DMSO-d6) = 5.10 (2H, s) ; 6.85-7.10 (6H, m) ; 7.10-7.25 (2H, m) ; 7.40-7.50 (1H, m) ; 7.80-8.10 (2H, m) ; 8.50-8.75 (2H, m)
29a	388724	O	3-pyridyl	1	4-cyano	(DMSO-d6) = 5.14 (2H, m) ; 6.80-7.00 (2H, m) ; 7.00-7.25 (4H, m) ; 7.35-7.65 (3H, m) ; 7.80-8.00 (1H, m) ; 8.45-8.85 (3H, m)
30a	388725	O	3-pyridyl	1	4-OCF_3	(DMSO-d6) = 5.11 (2H, m) ; 6.85-7.25 (8H, m) ; 7.35-7.55 (1H, m) ; 7.80-8.00 (1H, m) ; 8.00-8.25 (1H, m) ; 8.50-8.80 (2H, m)
31a	388726	O	3-pyridyl	1	3-cyano	(DMSO-d6) = 5.13 (2H, s) ; 7.00-7.25 (7H, m) ; 7.25-7.50 (2H, m) ; 7.80-7.95 (1H, m) ; 8.25-8.40 (1H, m) ; 8.50-8.75 (2H, m)
32a	388727	O	3-pyridyl	1	3-CF_3	(DMSO-d6) = 5.12 (2H, m) ; 6.90-7.25(7H, m) ; 7.25-7.50 (2H, m) ; 7.80-7.95 (1H, m) ; 8.20-8.35 (1H, m) ; 8.50-8.75 (2H, m)
33a	388729	O	3-pyridyl	1	4-SCH_3	(DMSO-d6) = 2.38 (3H, s) ; 5.12 (2H, s) ; 6.85-7.10 (6H, m) ; 7.10-7.25 (2H, m) ; 7.40-7.50 (1H, m) ; 7.80-8.00 (2H, m) ; 8.50-8.70 (2H, m)

The compounds in Table 4 correspond to the following formula:

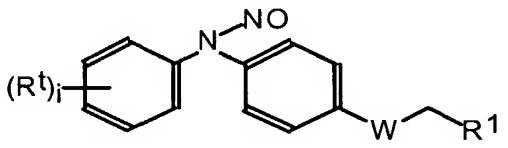
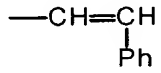
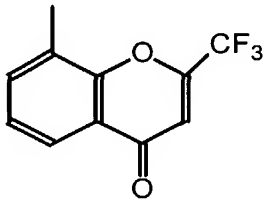


TABLE 4

Example No.	Reference	W	R^1	i	R^t	NMR
3b	LR 21062	O	4-methoxyphenyl	1	4-OCH_3	(DMSO-d6) = 3.70-3.90 (6H, 4s) ; 5.06 (2H, s) ; 6.90-7.00 (2H, m) ; 7.00-7.20 (6H, m) ; 7.28-7.48 (4H, m)
4b	LR 21063	O	3-trifluoromethyl-phenyl	1	4-OCH_3	(DMSO-d6) = 3.80 (3H, s) ; 5.27 (2H, s) ; 6.95-7.25 (6H, m) ; 7.25-7.40 (2H, m) ; 7.60-7.88 (4H, m)
5b	LR 21064	O	phenyl	1	4-OCH_3	(DMSO-d6) = 3.80 (3H, 2s) ; 5.15 (2H, s) ; 7.00-7.25 (6H, m) ; 7.25-7.55 (7H, m)
6b	LR 21068	O		1	4-OCH_3	(DMSO-d6) = 3.80 (3H, 2s) ; 4.78 (2H, broad m) ; 6.40-6.64 (1H, m) ; 6.70-7.00 (1H, m) ; 7.00-7.20 (6H, m) ; 7.20-7.43 (5H, m) ; 7.43-7.60 (2H, m)
7b	LR 21069	O	4-methoxycarbon-ylphenyl	1	4-OCH_3	(DMSO-d6) = 3.79 (3H, 2s) ; 3.85 (3H, s) ; 5.26 (2H, 2s) ; 7.00-7.20 (6H, m) ; 7.30-7.40 (2H, m) ; 7.55-7.70 (2H, m) ; 7.95-8.05 (2H, m)
8b	LR 21092	O	1-naphthyl	1	4-OCH_3	(DMSO-d6) = 3.80 (3H, 2s) ; 5.60 (2H, 2s) ; 7.00-7.15 (4H, m) ; 7.15-7.45 (4H, m) ; 7.45-7.80 (4H, m) ; 7.90-8.20 (3H, m)
9b	LR 21093	O	2-methylphenyl	1	4-OCH_3	(DMSO-d6) = 2.34 (3H, 2s) ; 3.81 (3H, 2s) ; 5.13 (2H, 2s) ; 7.00-7.30 (9H, m) ; 7.30-7.50 (3H, m)
10b	LR 21094	O	2-fluorophenyl	1	4-OCH_3	(DMSO-d6) = 3.79 (3H, 2s) ; 5.19 (2H, s) ; 6.95-7.75 (12H, m)
11b	LR 21095	O	4-fluorophenyl	1	4-OCH_3	(DMSO-d6) = 3.80 (3H, 2s) ; 5.13 (2H, 2s) ; 7.00-7.45 (10H, m) ; 7.45-7.65 (2H, m)

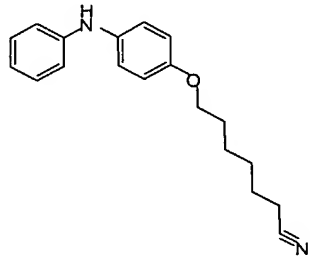
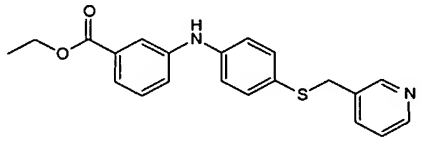
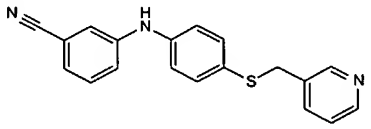
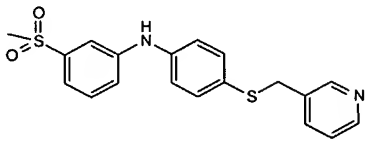
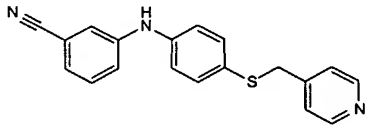
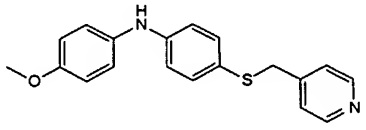
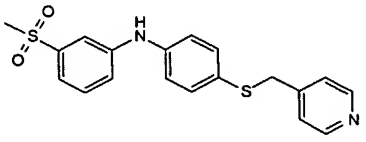
12b	LR 21096	O	4-ethylphenyl	1	4-OCH_3	(DMSO-d6) = 1.18 (3H, t, J=7.6 Hz) ; 2.62 (2H, q, J=7.6 Hz) ; 3.79 (3H, 2s) ; 5.10 (2H, s) ; 6.95-7.60 (12H, m)
13b	LR 21097	O	2-chlorophenyl	1	4-OCH_3	(DMSO-d6) = 3.79 (3H, 2s) ; 5.20 (2H, 2s) ; 7.00-7.30 (6H, m) ; 7.30-7.75 (6H, m)
14b	LR 21098	O	4-chlorophenyl	1	4-OCH_3	(DMSO-d6) = 3.80 (3H, 2s) ; 5.15 (2H, 2s) ; 7.00-7.25 (6H, m) ; 7.25-7.40 (2H, m) ; 7.40-7.60 (4H, m)
15b	LR 21099	O	4-trifluoromethyl-phenyl	1	4-OCH_3	(DMSO-d6) = 3.80 (3H, 2s) ; 5.28 (2H, s) ; 7.00-7.30 (6H, m) ; 7.30-7.40 (2H, m) ; 7.60-7.95 (4H, m)
16b	LR 21100	O	4-cyanophenyl	1	4-OCH_3	(DMSO-d6) = 3.79 (3H, 2s) ; 5.28 (2H, s) ; 6.95-7.25 (6H, m) ; 7.25-7.40 (2H, m) ; 7.60-7.75 (2H, m) ; 7.80-8.00 (2H, m)
17b	LR 20784	O	2-cyanophenyl	0	-	(DMSO-d6) =5.30 (2H, 2s) ; 7.10-7.35 (3H, m) ; 7.35-7.70 (6H, m) ; 7.70-8.05 (4H, m)
18b	LR 21101	O	2,4-dichlorophenyl	1	4-OCH_3	(DMSO-d6) = 3.80 (3H, 2s) ; 5.19 (2H, 2s) ; 7.00-7.25 (6H, m) ; 7.25-7.40 (2H, m) ; 7.40-7.55 (1H, m) ; 7.55-7.75 (2H, m)
19b	LR 21156	O	7-methoxycoumarin-4-yl	1	4-OCH_3	(DMSO-d6) = 3.80 (3H, 2s) ; 3.88 (3H, s) ; 5.45 (2H, s) ; 6.43 (1H, m) ; 6.90-7.65 (10H, m) ; 7.65-10.0 (1H, m)
20b	LR 21157	O	2-phenyl-5-methyl oxazol-4-yl	1	4-OCH_3	(DMSO-d6) = 2.46 (3H, 2s) ; 3.80 (3H, 2s) ; 5.07 (2H, 2s) ; 6.95-7.30 (6H, m) ; 7.30-7.45 (2H, m) ; 7.45-7.70 (3H, m) ; 7.82-8.10 (2H, m)

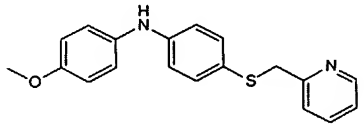
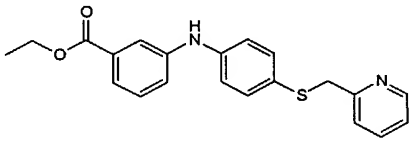
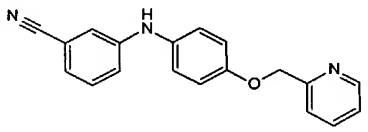
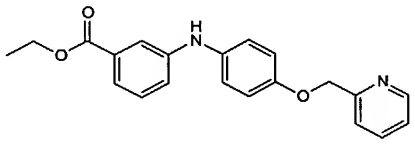
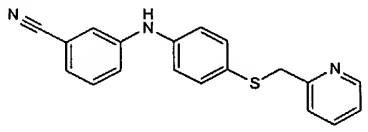
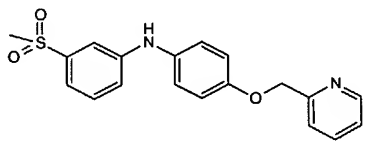
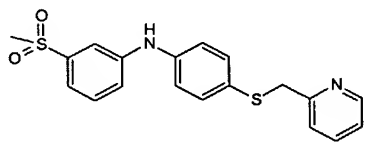
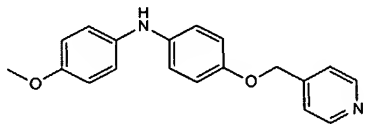
21b	LR 21158	O	2-ethoxycarbonyl-5-benzofuryl	1	4-OCH_3	(DMSO-d6) = 1.34 (3H, t, J=7.06 Hz) ; 3.80 (3H, 2s) ; 4.37 (2H, q, J=7.06 Hz) ; 5.26 (2H, s) ; 6.95-7.30 (6H, m) ; 7.30-7.45 (2H, m) ; 7.45-8.05 (4H, m)
22b	LR 21159	O		1	4-OCH_3	(DMSO-d6) = 3.80 (3H, 2s) ; 5.42 (2H, 2s) ; 7.00-7.30 (7H, m) ; 7.30-7.45 (2H, m) ; 7.55-7.75 (1H, m) ; 7.95-8.25 (2H, m)
23b	LR 21177	O	2-methoxy-5-acetyl-phenyl	1	4-OCH_3	(DMSO-d6) = 2.52 (3H, 2s) ; 3.80 (3H, 2s) ; 3.92 (3H, s) ; 5.13 (2H, s) ; 6.95-7.30 (7H, m) ; 7.30-7.45 (2H, m) ; 7.95-8.15 (2H, m)
24b	LR 21201	O	quinolyl-2-yl	1	4-OCH_3	(DMSO-d6) = 3.79 (3H, 2s) ; 5.42 (2H, s) ; 7.00-7.15 (4H, m) ; 7.15-7.40 (4H, m) ; 7.55-7.90 (3H, m) ; 7.95-8.15 (2H, m) ; 8.35-8.55 (1H, m)
25b	LR 21144	O	diisopropylamino-methyl	1	4-OCH_3	(DMSO-d6) = 0.99 (12H, 2d, J=6.56 Hz) ; 2.77 (2H, 2t, J=7.08 Hz) ; 3.01 (2H, septet, J=6.56 Hz) ; 3.79 (3H, 2s) ; 3.90 (2H, 2t, J=7.08 Hz) ; 6.95-7.20 (6H, m) ; 7.25-7.45 (2H, m)
26b	388718	S	3-pyridyl	1	4-OCH_3	(DMSO-d6) = 3.80 (3H, 2s) ; 4.33 (2H, 2s) ; 7.00-7.20 (4H, m) ; 7.20-7.60 (5H, m) ; 7.70-7.90 (1H, m) ; 8.35-8.65 (2H, m)
27b	390417	O	3-pyridyl	1	4-methyl	(DMSO-d6) = 2.35 (3H, 2s) ; 5.34 (2H, 2s) ; 7.00-7.25 (4H, m) ; 7.25-7.55 (5H, m) ; 7.80-8.00 (1H, m) ; 8.40-8.85 (2H, m)

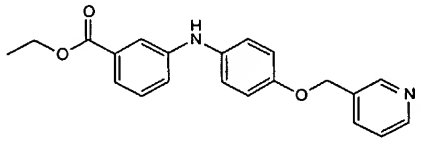
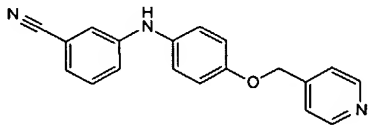
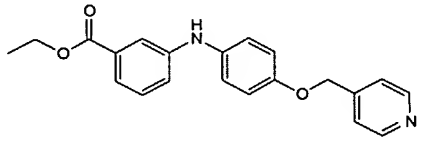
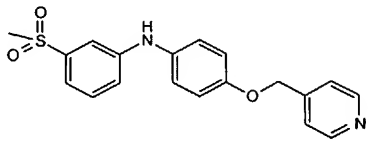
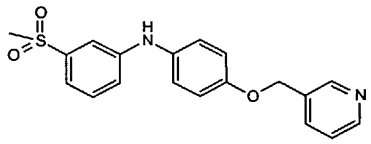
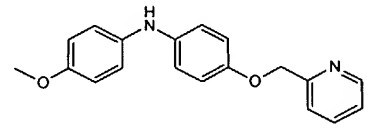
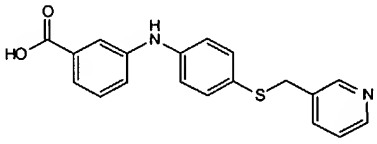
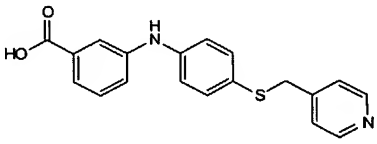
28b	390419	O	3-pyridyl	1	4-chloro	(DMSO-d6) = 5.22 (2H, 2s) ; 7.05-7.35 (4H, m) ; 7.35-7.50 (3H, m) ; 7.50-7.70 (2H, m) ; 7.80-8.00 (1H, m) ; 8.50-8.80 (2H, m)
29b	390420	O	3-pyridyl	1	4-cyano	(DMSO-d6) = 5.23 (2H, m) ; 7.10-7.35 (4H, m) ; 7.35-7.70 (3H, m) ; 7.80-8.10 (3H, m) ; 8.50-8.85 (2H, m)
30b	390421	O	3-pyridyl	1	4-OCF_3	(DMSO-d6) = 5.22 (2H, 2s) ; 7.10-7.30 (3H, m) ; 7.30-7.70 (6H, m) ; 7.80-8.00 (1H, m) ; 8.50-8.80 (2H, m)
31b	390422	O	3-pyridyl	1	3-cyano	(DMSO-d6) = 5.22 (2H, s) ; 7.10-7.30 (3H, m) ; 7.40-7.60 (2H, m) ; 7.65-7.80 (2H, m) ; 7.80-8.05 (3H, m) ; 8.55-8.75 (2H, m)
32b	390423	O	3-pyridyl	1	3-CF_3	(DMSO-d6) = 5.22 (2H, 2s) ; 7.15-7.35 (3H, m) ; 7.35-7.60 (2H, m) ; 7.60-8.00 (5H, m) ; 8.50-8.80 (2H, m)
33b	390424	O	3-pyridyl	1	4-SCH_3	(DMSO-d6) =2.48 (3H, 2s) ; 5.20 (2H, 2s) ; 7.00-7.55 (9H, m) ; 7.75-8.00 (1H, m) ; 8.45-8.80 (2H, m)

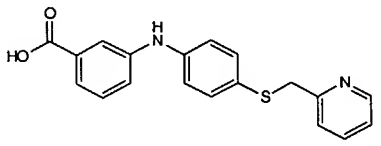
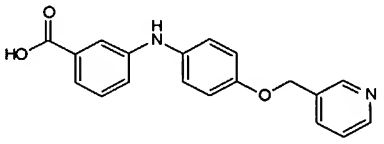
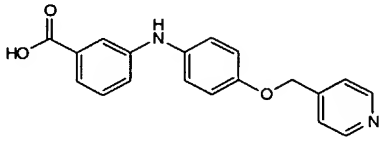
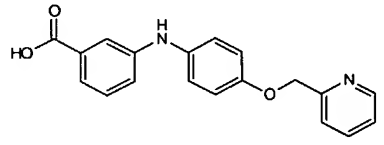
The compounds of Examples 36 to 56 were obtained as in Example 1.

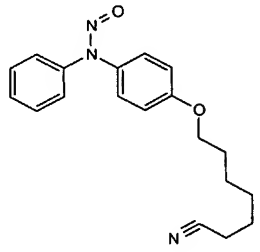
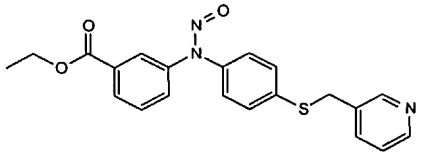
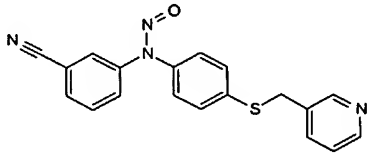
The compounds of Examples 57 to 62 were obtained as in Example 2.

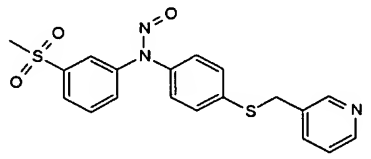
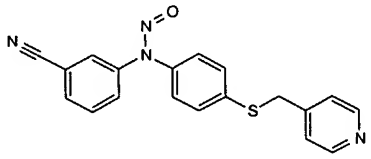
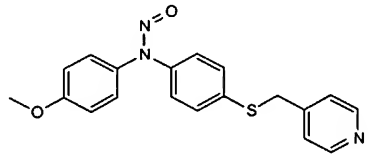
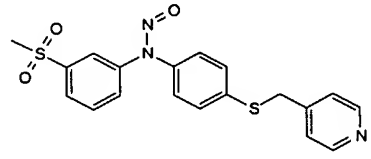
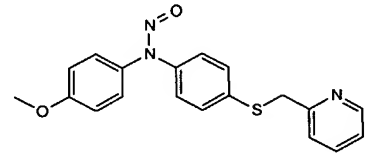
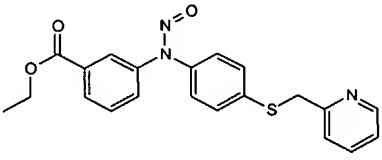
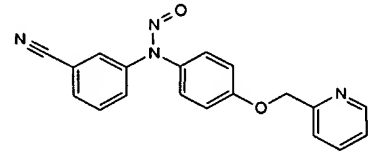
Examples CHEMISTRY		NMR
36 a		(DMSO-d6) : 1.30-1.82 (8H, m) ; 2.38-2.58 (2H, m) ; 3.78-4.01 (2H, m) ; 6.55-7.29 (9H, m) ; 7.81 (1H, s).
37 a		(Acetone-d6) : 1.22-1.40 (3H, m) ; 4.09 (2H, s) ; 4.17-4.43 (2H, m) ; 6.88-7.87 (11H, m) ; 8.24-8.59 (2H, m).
38 a		(Acetone-d6) :4.11 (2H, s) ; 6.98-7.49 (9H, m) ; 7.56-7.69 (1H, m) ; 7.79-7.93 (1H, m) ; 8.31-8.46 (2H, m) .
39 a		(Acetone-d6) : 3.09 (3H, s) ; 4.12 (2H, s) ; 7.05-7.75 (10H, m) ; 7.87-7.97 (1H, m) ; 8.32-8.46 (2H, m).
40 a		(Acetone-d6) : 4.09 (2H, s) ; 6.91-7.55 (10H, m) ; 7.88 (1H, broad s) ; 8.29-8.58 (2H, m).
41 a		(Acetone-d6) : 3.58 (3H, s) ; 3.80 (2H, s) ; 6.48-7.28 (11H, m) ; 8.10-8.37 (2H, m).
42 a		(Acetone-d6) : 3.09 (3H, s) ; 4.09 (2H, s) ; 6.93-7.72 (10H, m) ; 7.93 (1H, broad s) ; 8.31-8.60 (2H, m).

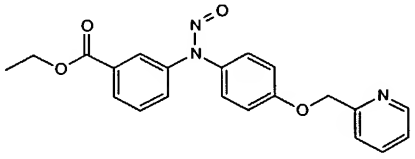
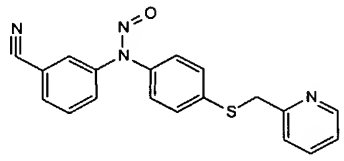
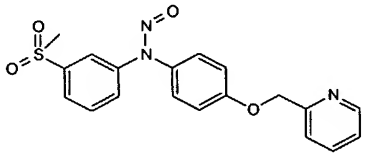
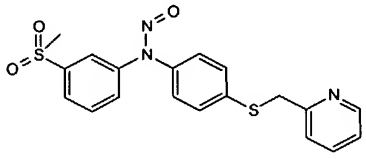
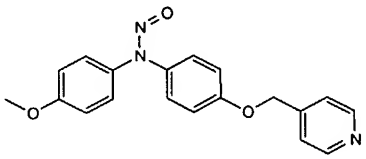
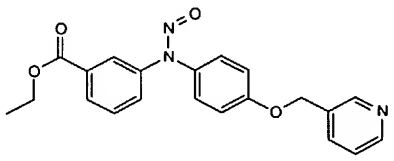
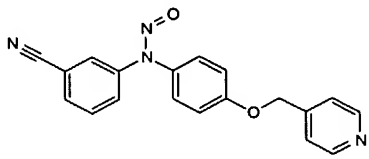
43 a		(Acetone-d6) : 4.21 (3H, s) ; 4.55 (2H, s) ; 6.93-7.83 (11H, m) ; 8.10 (1H, broad s) ; 8.78-8.99 (1H, m).
44 a		(Acetone-d6) : 1.13-1.67 (3H, m) ; 4.21 (2H, s) ; 4.23-4.48 (2H, m) ; 6.81-7.91 (12H, m) ; 8.49 (1H, broad s).
45 a		(Acetone-d6) : 5.17 (2H, s) ; 6.85-7.64 (11H, m) ; 7.68-7.91 (1H, m) ; 8.38-8.71 (1H, m).
46 a		(Acetone-d6) : 1.10-1.43 (3H, m) ; 4.20-4.39 (2H, m) ; 5.16 (2H, s) ; 6.78-7.89 (12H, m) ; 8.56 (1H, broad s).
47 a		(Acetone-d6) : 4.66 (2H, s) ; 7.37-7.97 (10H, m) ; 7.99-8.41 (2H, m) ; 8.91 (1H, broad s).
48 a		(Acetone-d6) : 2.27 (3H, s) ; 4.39 (2H, s) ; 6.03-7.14 (12H, m) ; 7.61-7.90 (1H, m).
49 a		(Acetone-d6) : 3.06 (3H, s) ; 4.21 (2H, s) ; 6.93-8.01 (12H, m) ; 8.46 (1H, broad s).
50 a		(Acetone-d6) : 3.73 (3H, s) ; 5.12 (2H, s) ; 6.52-7.21 (9H, m) ; 7.27-7.59 (2H, m) ; 8.40-8.75 (2H, m).

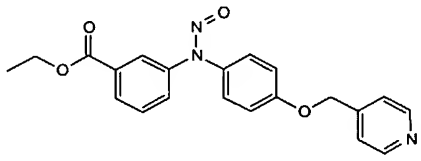
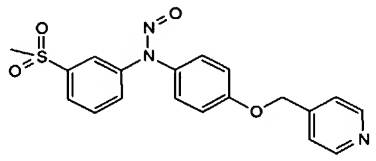
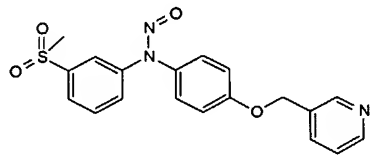
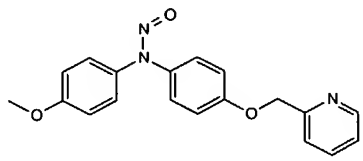
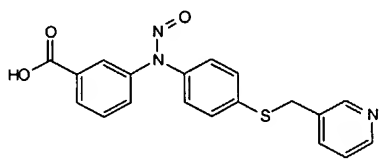
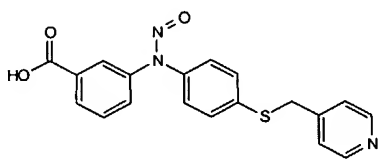
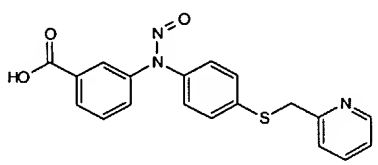
51 a		(Acetone-d6) : 1.07-1.45 (3H, m) ; 4.04-4.46 (2H, m) ; 5.15 (2H, s) ; 6.67-8.01 (11H, m) ; 8.37-8.87 (2H, m).
52 a		(Acetone-d6) : 5.19 (2H, s) ; 6.73-7.80 (11H, m) ; 8.35-8.74 (2H, m).
53 a		(Acetone-d6) : 1.01-1.51 (3H, m) ; 4.14-4.45 (2H, m) ; 5.17 (2H, s) ; 6.75-7.85 (11H, m) ; 8.35-8.74 (2H, m).
54 a		(Acetone-d6) : 3.05 (3H, s) ; 5.19 (2H, s) ; 6.84-7.77 (11H, m) ; 8.38-8.76 (2H, m).
55 a		(Acetone-d6) : 3.05 (3H, s) ; 5.17 (2H, s) ; 3.86-7.97 (11H, m) ; 8.38-8.83 (2H, m) .
56 a		(Acetone-d6) : 3.73 (3H, s) ; 5.11 (2H, s) ; 6.57-7.10 (9H, m) ; 7.17-7.38 (1H, m) ; 7.44-7.64 (1H, m) ; 7.68-7.88 (1H, m) ; 8.55 (1H, broad s).
57 a		(Acetone-d6) : 4.09 (2H, s) ; 6.89-7.90 (11H, m) ; 8.28-8.55 (2H, m) ; 11.29 (1H, broad s).
58 a		(Acetone-d6) : 4.07 (2H, s) ; 6.87-7.53 (11H, m) ; 7.74 (1H, broad s) ; 8.25-8.52 (2H, m).

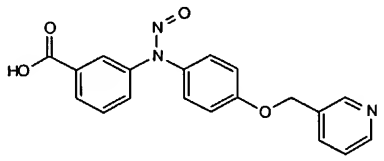
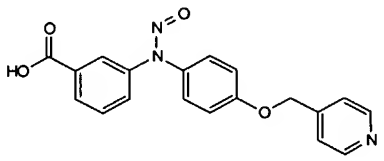
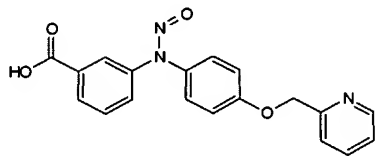
59 a		(Acetone-d6) : 4.18 (2H, s) ; 6.87-7.81 (12H, m) ; 8.32-8.52 (1H, m) ; 11.22 (1H, broad s).
60 a		(Acetone-d6) : 5.15 (2H, s) ; 6.83-7.51 (10H, m) ; 7.54-8.05 (1H, m) ; 8.38-8.82 (2H, m) ; 11.12 (1H, broad s).
61 a		(Acetone-d6) : 5.62 (2H, s) ; 7.25-8.33 (11H, m) ; 8.85-9.16 (2H, m) ; 12.93 (1H, broad s).
62 a		(DMSO-d6) : 5.13 (2H, s) ; 6.83-7.62 (10H, m) ; 7.74-7.94 (1H, m) ; 8.00-8.16 (1H, m) ; 8.47-8.69 (1H, m) ; 12.75 (1H, broad s).

36 b		(DMSO-d6) : 1.37-1.87 (8H, m) ; 2.40-2.57 (2H, m) ; 3.93-4.21 (2H, m) ; 6.96-7.82 (9H, m).
37 b		(Acetone-d6) : 1.24-1.41 (3H, m) ; 4.04-4.13 (4H, m) ; 7.03-7.82 (10H, m) ; 7.96-8.16 (1H, m) ; 8.36-8.64 (1H, m).
38 b		(Acetone-d6) : 4.30 and 4.36 (2H, 2s) ; 7.03-7.99 (10H, m); 8.35-8.65 (2H, m).

39 b		(Acetone-d6) : 3.18 (3H, 2s) ; 4.30 and 4.36 (2H, 2s) ; 7.07-8.12 (10H, m) ; 8.37-8.65 (2H, m).
40 b		(Acetone-d6) : 4.29 and 4.35 (2H, 2s) ; 6.70-8.18 (10H, m) ; 8.24-8.80 (2H, m).
41 b		(Acetone-d6) : 3.85 (3H, s) ; 4.26 and 4.31 (2H, 2s) ; 6.77-7.80 (10H, m) ; 8.32-8.62 (2H, m).
42 b		(Acetone-d6) : 3.63 (3H, s) ; 4.74 and 4.79 (2H, 2s) ; 7.26-8.72 (10H, m) ; 8.72-9.24 (2H, m).
43 b		(Acetone-d6) : 3.84 and 3.86 (3H, 2s) ; 4.34 and 4.39 (2H, 2s) ; 6.81-7.58 (10H, m) ; 7.63-7.79 (1H, m) ; 8.40-8.54 (1H, m).
44 b		(Acetone-d6) : 1.18-1.45 (3H, m) ; 4.22-4.46 (4H, m) ; 6.94-7.81(10H, m) ; 7.91-8.19 (1H, m) ; 8.42-8.56 (1H, m).
45 b		(Acetone-d6) : 5.25 and 5.27 (2H, 2s) ; 7.00-7.94 (11H, m) ; 8.49-8.64 (1H, m).

46 b		(Acetone-d6) : 1.82-2.16 (3H, m) ; 4.90-5.17 (2H, m) ; 5.94 and 5.97 (2H, 2s) ; 7.64-8.89 (11H, m) ; 9.18-9.35 (1H, m).
47 b		(Acetone-d6) : 4.36 and 4.41 (2H, 2s) ; 7.01-7.97 (11H, m) ; 8.42-8.57 (1H, m).
48 b		(Acetone-d6) : 3.17 (3H, s) ; 5.25 and 5.27 (2H, 2s) ; 7.04-8.10 (11H, m) ; 8.50-8.64 (1H, m).
49 b		(Acetone-d6) : 3.18 (3H, s) ; 4.36 and 4.41 (2H, 2s) ; 6.95-8.21 (11H, m) ; 8.34-8.62 (1H, m).
50 b		(Acetone-d6) : 3.84 (3H, s) ; 5.26 (2H, s) ; 6.65-7.73 (10H, m) ; 8.38-8.75 (2H, m).
51 b		(Acetone-d6) : 1.02-1.68 (3H, m) ; 4.18-4.50 (2H, m) ; 5.28 (2H, s) ; 6.84-8.20 (10H, m) ; 8.41-8.83 (2H, m).
52 b		(Acetone-d6) : 5.29 (2H, s) ; 6.89-8.18 (10H, m) ; 8.42-8.74 (2H, m).

53 b		(Acetone-d6) : 1.13-1.51 (3H, m) ; 4.22-4.47 (2H, m) ; 5.29 (2H, s) ; 6.84-7.83 (9H, m) ; 7.85-8.17 (1H, m) ; 8.41-8.74 (2H, m).
54 b		(Acetone-d6) : 3.17 (3H, s) ; 5.29 (2H, s) ; 6.90-8.18 (10H, m) ; 8.45-8.79 (2H, m).
55 b		(Acetone-d6) : 3.18 (3H, s) ; 5.26 (2H, s) ; 7.01-8.10 (10H, m) ; 8.46 8.81 (2H, m).
56 b		(Acetone-d6) : 3.82 and 3.84 (3H, 2s) ; 5.22 and 5.23 (2H, 2s) ; 6.95-7.42 (9H, m) ; 7.49-7.63 (1H, m) ; 7.73-7.90 (1H, m) ; 8.51-8.62 (1H, m).
57 b		(Acetone-d6) : 4.30 and 4.36 (2H, 2s) ; 7.21-8.21 (11H, m) ; 8.34-8.68 (2H, m).
58 b		(Acetone-d6) : 4.27 and 4.33 (2H, 2s) ; 6.99-8.22 (10H, m) ; 8.33-8.61 (2H, m) ; 11.39 (1H, broad s).
59 b		(Acetone-d6) : 4.38 and 4.43 (2H, 2s) ; 6.91-7.83 (10H, m) ; 7.86-8.17 (1H, m) ; 8.41-8.63 (1H, m) ; 13.11 (1H, broad s).

60 b		(DMSO-d6) : 5.70 (2H, s) ; 7.45-8.60 (10H, m) ; 8.90-9.31 (2H, m) ; 13.52 (1H, broad s).
61 b		(DMSO-d6) : 5.25 (2H, s) , 7.06-8.07 (10H, m) ; 8.48-8.69 (2H, m) ; 13.25 (1H, broad s).
62 b		(DMSO-d6) : 5.23 and 5.25 (2H, 2s) ; 7.00-8.14 (11H, m) ; 8.43-8.69 (1H, m) ; 13.27 (1H, broad s).

Example 63

4-{Nitroso[4-(pyrid-4-ylmethoxy)phenyl]amino}benzamide

a) 3-{[4-(Pyrid-4-ylmethoxy)phenyl]amino}benzamide

Obtained after purification by chromatography on a column of silica with an ethyl acetate/heptane mixture (6/4) from the crude reaction mixture of Example 52a.

Yield : 14%

NMR (DMSO-d6) : 5.1 (2H, s) ; 6.8-7.65 (11H, m) ; 7.7-7.9 (1H, m) ; 7.8 (1H, s) ; 8.35 (2H, m); 7.9-8.1 (1H, m); 8.6 (2H, broad s)

b) 4-{Nitroso[4-(pyrid-4-ylmethoxy)phenyl]amino}benzamide

Obtained by working as in Example 1b.

Yield : 75%

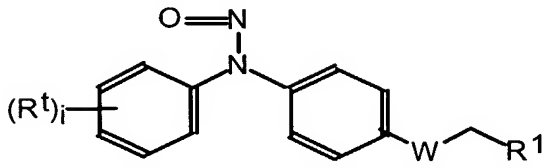
NMR (acetone-d6) : 5.25 (2H, 2s); 6.6-8.1 (12H, m); 8.6 (2H, broad s).

Biological results

Examples	Nitrites + nitrates (μM)	Antioxidant effect IC_{50} (μM)
36a	-	7.5
41a	-	4.4
41b	49	5.3
43a	-	2.5
48a	-	11.8
48b	94	11.9
50a	-	6.1
50b	66	3.8
56a	-	6.6
56b	62	7.6
63a	-	7.5
63b	56	15.6

CLAIMS

1. Compounds of the formula I :



I

in which:

- W represents O or S;

- the radicals R^t, which may be identical or different, represent a halogen atom; a saturated or unsaturated aliphatic hydrocarbon group, optionally interrupted with O and/or S and optionally halogenated; nitro; carboxyl or cyano;

- i represents an integer from 0 to 5, preferably 0, 1 or 2;

- R^1 represents an optionally substituted saturated, unsaturated and/or aromatic heterocyclic radical; an optionally substituted saturated, unsaturated and/or aromatic carbocyclic radical; -E-Q, in which E represents optionally substituted alkylene or alkenylene and Q represents an amino group which is optionally substituted by one or two saturated or unsaturated aliphatic hydrocarbon groups; or -E-Ar, in which E is as defined above and Ar represents an optionally substituted saturated, unsaturated and/or aromatic carbocyclic radical or alternatively an optionally substituted saturated, unsaturated and/or aromatic heterocyclic radical; or an optionally halogenated, saturated aliphatic hydrocarbon group;

with the exclusion of the compounds of the formula I in which i is 1; R^t represents 2-methyl and R^1 represents $-CH_3$,

and their pharmaceutically tolerable derivatives, solvates and stereoisomers.

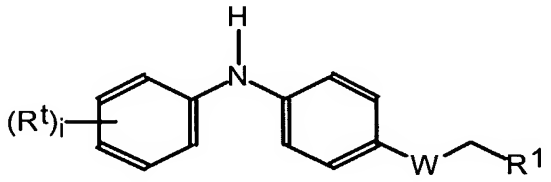
2. Compound according to Claim 1, characterized in that R^1 represents an optionally substituted aromatic carbocyclic radical; an optionally substituted aromatic heterocyclic radical; an optionally substituted heterocyclic radical with an aromatic moiety; -E-Q, in which E represents alkylene and Q represents

amino, alkylamino or dialkylamino; or -E-Ar, in which E represents alkenylene and Ar represents an optionally substituted aromatic carbocyclic radical, an optionally substituted aromatic heterocyclic radical or a radical with an optionally substituted aromatic moiety.

3. Compound according to Claim 2, characterized in that R^1 represents optionally substituted phenyl; optionally substituted naphthyl; optionally substituted pyridyl; optionally substituted quinolyl; optionally substituted benzofuryl; optionally substituted oxazolyl; aminoalkyl; alkylaminoalkyl; dialkylaminoalkyl; optionally substituted coumarinyl; phenylalkenylene in which the phenyl nucleus is optionally substituted; 4-oxo-4H-benzopyranyl.

4. Compound of the formula I according to any one of Claims 1 to 3, characterized in that the radical R^1 comprises at least one carbocyclic or heterocyclic nucleus which is substituted by one or more substituents chosen from oxo; optionally halogenated alkyl; optionally halogenated alkoxy; cyano; halogen; carboxyl; alkylcarbonyl; alkoxycarbonyl; and optionally substituted aryl.

5. Process for preparing a compound of the formula I according to any one of Claims 1 to 4, characterized in that a nitrosating agent, such as an alkali metal nitrite, is reacted with a compound of the formula II:

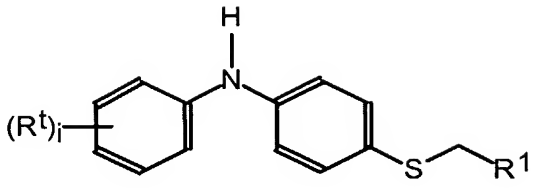


II

in which i, R^t, W and R^1 are as defined for formula I.

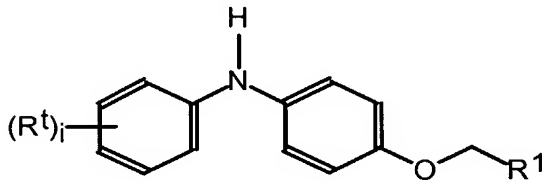
6. Process according to Claim 5, characterized in that the reaction is carried out in a mixture of acetic acid and water, at a temperature of between 10 and 30°C and preferably between 15 and 25°C.

7. Compound of the formula II :



in which i, R^t and R^1 are as defined according to any one of Claims 1 to 5.

8. Compound of the formula IIa :



IIa

in which i and R^t are as defined in Claim 1 and R^1 represents optionally substituted naphthyl; unsubstituted pyridyl; optionally substituted coumarinyl; optionally substituted oxazolyl; optionally substituted benzoxazolyl; optionally substituted benzofuryl; optionally substituted 4-oxo-4H-benzopyranyl; cinnamyl which is optionally substituted on the phenyl nucleus; aminoalkyl; alkylaminoalkyl; or dialkylaminoalkyl; phenyl which is substituted by one or more substituents chosen from the following groups: cyano; carboxyl; nitro; halogenated (C_1-C_4)alkoxy (and preferably trifluoromethoxy); optionally halogenated (C_1-C_{14})-thioalkoxy, preferably (C_1-C_{10})thioalkoxy; halogenated and preferably perhalo (C_1-C_{14})alkyl (and especially trifluoromethyl); (C_1-C_{14})alkylcarbonyl in which the alkyl moiety is optionally halogenated; (C_1-C_{14})alkoxycarbonyl in which the alkoxy moiety is optionally halogenated; (C_6-C_{18})arylcarbonyl in which the aryl moiety is optionally substituted one or more times by halogen, optionally halogenated (C_1-C_{14})alkyl and optionally halogenated (C_1-C_{14})alkoxy; (C_1-C_{14})-alkylcarbonylamino in which the alkyl moiety is optionally halogenated; (C_6-C_{18})-arylcarbonylamino in which the aryl is optionally substituted one or more times by halogen, optionally halogenated (C_1-C_{14})alkyl and optionally halogenated (C_1-C_{14})alkoxy; and (C_6-C_{18})aryl which is optionally substituted one or more times by halogen, optionally halogenated (C_1-C_{14})alkyl, such as trifluoromethyl, and optionally halogenated (C_1-C_4)alkoxy, such as trifluoromethoxy;

with the exclusion of the compounds of the formula IIa in which R^1 represents dimethylaminomethyl; dimethylaminoethyl; and diethylaminomethyl.

9. Pharmaceutical composition comprising at least one compound of the formula I according to any one of Claims 1 to 4, in combination with one or more pharmaceutically acceptable excipients.

10. Pharmaceutical composition comprising at least one compound of the formula II according to either of Claims 7 and 8, in combination with one or more pharmaceutically acceptable excipients.

11. Use of a compound of the formula I according to any one of Claims 1 to 4, for the preparation of a medicinal product that may be used in the treatment of pathologies characterized by an oxidative stress condition and a lack of availability of endothelial nitrogen monoxide.

12. Use of a compound of the formula II according to either of Claims 7 and 8, for the preparation of an antioxidant medicinal product as a free-radical scavenger.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 02/10607

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D213/30 A61P9/00 A61P7/00 A61K31/4406 C07C211/55
C07C243/06 C07D311/16 C07D311/22 C07D263/32 C07D307/85
C07D215/14 C07D213/32

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D C07C A61P A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data, EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PATENT ABSTRACTS OF JAPAN vol. 018, no. 615 (C-1277), 24 November 1994 (1994-11-24) & JP 06 234718 A (SUMITOMO CHEM CO LTD), 23 August 1994 (1994-08-23) abstract ---	1
A	WO 00 61541 A (NICOX SA ;DEL SOLDATO PIERO (IT)) 19 October 2000 (2000-10-19) the whole document ---	1,9-12
A	PATENT ABSTRACTS OF JAPAN vol. 1998, no. 09, 31 July 1998 (1998-07-31) & JP 10 087592 A (FUJIMORI KEN;DOUJIN KAGAKU KENKYUSHO:KK), 7 April 1998 (1998-04-07) abstract --- -/--	1

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 November 2002	04/12/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Bosma, P

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 02/10607

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
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